Original Communications

THE HEART IN RHEUMATOID ARTHRITIS

A STUDY OF THIRTY-EIGHT AUTOPSY CASES

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ALTHOUGH a common etiological background for chronic rheumatoid arthritis and rheumatic heart disease has been accepted in Europe, principally by German authors,[1-4] but also by some of the English,[5-10] French,[11-16] and Scandinavian writers,[17] this concept has by no means been established in this country. The prevailing opinion here has been that, when chronic structural joint changes and evidence of rheumatic carditis co-exist, it is a rather rare combination of two distinct clinical entities. The belief is that either they are present concurrently,[18, 19] or that the arthritis was preceded by acute or subacute rheumatic fever.[20, 21] The most recent *Primer on Arthritis*,[22] published by the American Rheumatism Association, holds this view.

Unfortunately, this concept of an etiological difference persists because of the lack of post-mortem studies of a sufficiently large number of patients with rheumatoid arthritis, for, as pointed out forty years ago by Pribram,[2] and later by Klinge,[4] the clinical diagnosis of heart disease in patients with arthritis is infrequently made. Baggenstoss and Rosenberg,[23] in reporting a series of twenty-five cases in which there were autopsies, found twenty cardiac lesions, fourteen of which were assumed to be rheumatic. The clinical diagnosis was made in *only* seven of these cases. In Bayles'[24] recent paper, of the six cases in which rheumatic heart disease was found at necropsy, the clinical diagnosis had been made in four.

It is the purpose of this report to present the post-mortem and related clinical data in thirty-eight cases of rheumatoid arthritis in adults. In

TABLE I

CLINICAL AND NECROPSY DATA IN THIRTY-THREE CASES OF RHEUMATOID ARTHRITIS AND HEART DISEASE

CASE	SEX	AGE OF ONSET OF JOINT DEFORMITY (YR.)	AGE COVERED HEART DISEASE (YR.)	AGE AT DEATH (YR.)	JOINT INVOLVEMENT			HEART INVOLVEMENT		CAUSE OF DEATH	OTHER PATHOLOGIC FINDINGS	MISCELLANEOUS
					TYPE OF ONSET	COURSE	DEFORMITY	CLINICAL	POST MORTEM			
1	M	17	35	63	Pain in right hip	Progressive, multiple deformity. Bedridden 35 years	Upper and lower extremities, spine	Enlarged heart M.S., M.I., A.I. B.P. 130/50	Weight 560 Gm. Healed rheumatic endocarditis of aortic valve. Calcification of aortic leaflets. Left auricular endocarditis	Congestive failure Bronchopneumonia	Left knee joint-cavity obliterated by fibrous ankylosis	Bilateral iritis
2	F	25	38	47	Acute phalangeal arthritis	Frequent episodes of polyarthritis. Bedridden 13 years	Upper and lower extremities, spine	Enlarged heart A.I. A.S. B.P. 170/94	Weight 330 Gm. Healed rheumatic endocarditis of mitral valve. Indeterminate endocarditis of mitral valve	Uremia Congestive failure Bronchopneumonia	Acute diffuse glomerulonephritis	
3	M	?	—	53	Rigidity of neck	Insidious, progressive multiple deformity	Fingers, wrists, elbows, shoulders, knees, spine	Heart sounds poor and distant. B.P. 110/70	Weight 220 Gm. Adhesive pericarditis. Aortic valve slightly thickened	Bronchopneumonia	Amyloidosis of liver and spleen	
4	F	5	—	48	Painful swelling of toe in 2nd month of pregnancy	Post-partum multiple involvement. Recurrence with progressive deformity	Spine, upper and lower extremities except hips and shoulders	"No evidence of organic heart disease." B.P. 110/70 ECG—L.A.D.	Obliterative pericarditis	Bronchopneumonia		

5	M	20	38	49	Acute polyarthritis	Progressive pain and rigidity of spine. Insidious deformity	Spine (marked), hips, knees, shoulders	Enlarged heart A.I. B.P. 130/10 ECG—L.A.D. T_1, T_2 inverted, P.R. 0.25	Weight 850 Gm. Healed rheumatic endocarditis of aortic valve	Congestive failure	Acute nephritis Calcification of spinal ligaments	
6	F	35	—	48	Pain in ankles	Multiple, insidious deformity. Acute episode at 46 years of age	Upper and lower extremities	Heart sounds distant B.P. 88/50	Weight 300 Gm. Obliterative pericarditis	Bronchopneumonia		
7	M	29		32	Painless swelling right knee	Insidious, progressive, multiple deformity	Spine (marked), upper and lower extremities		Weight 330 Gm. Healed rheumatic endocarditis of mitral and aortic valves. Indeterminate endocarditis of mitral and aortic valves	Pulmonary infarct Bronchopneumonia	Amyloidosis of liver, spleen, and adrenals	Emaciation Premature senility
8	M	44	52	52	"Swollen hands"	Progressive insidious, multiple deformity	Upper and lower extremities	Enlarged heart M.I., A.I. B.P. 125/50	Weight 400 Gm. Healed rheumatic endocarditis of mitral valve. Slight thickening base of aortic valve	Pulmonary edema Carcinoma	Carcinoma of kidney with metastases	
9	F	32	39	39	Acute polyarthritis	Acute exacerbations with progressive deformity	Fingers, shoulders, elbows, knees, ankles	Feeble heart sounds, tachycardia B.P. 120/80	Weight 250 Gm. Acute rheumatic pericarditis	Rheumatic fever Congestive failure		Rheumatic fever
10	F	52	56	66	Acute polyarthritis	Progressive deformity. Bedridden 9 years	Spine (marked), upper and lower extremities	Enlarged heart M.I.	Weight 220 Gm. Chronic adhesive pericarditis. Healed rheumatic endocarditis of mitral, aortic and tricuspid valves. Left and right auricular endocarditis	Pulmonary tuberculosis	Amyloidosis of liver and kidneys Left knee joint—fibrous obliteration of cavity; bone atrophy	

TABLE I—CONT'D

	SEX	AGE OF ONSET OF JOINT DISEASE (YRS.)	AGE HEART DISEASE DISCOVERED (YRS.)	AGE AT DEATH (YRS.)	JOINT INVOLVEMENT TYPE OF ONSET	COURSE	DEFORMITY	HEART INVOLVEMENT CLINICAL	POST MORTEM	CAUSE OF DEATH	OTHER PATHOLOGIC FINDINGS	MISCELLANEOUS
	M	14	8	48	Acute rheumatic fever with joint and cardiac involvement	Recurrent rheumatic fever at 9, 10, and 11 years. Insidious, progressive deformity at 41 years of age	Hands, fingers, feet	Enlarged heart M.I., M.S., A.I., A.S. B.P. 168/68 ECG—L.A.D. auricular fibrillation and flutter	Weight 500 Gm. Focal adhesive pericarditis. Healed rheumatic endocarditis of mitral, aortic and tricuspid valves. Active endocarditis of mitral and aortic valves. Left and right auricular endocarditis. Calcification aortic leaflets	Cerebral embolus Bronchopneumonia Congestive failure	Amyloidosis of liver, spleen, kidneys, and adrenals	
12	F	44	33	60	Pain in left shoulder	Insidious, progressive, multiple deformity	Upper and lower extremities, spine	Enlarged heart A.I., M.I. R.P. 165/80; 170/100 ECG—L.A.D. high voltage, intraventricular block	Weight 400 Gm. Healed rheumatic endocarditis of mitral and aortic valves. Calcification base of aortic valve	Bronchopneumonia Congestive failure	Infarcts of spleen and kidneys	Hypertension Subcutaneous nodules
13	F	13		27	Acute arthritis left wrist with residual deformity	Acute episodes with deformity and ankylosis. Bedridden 4 years	Spine (marked), fingers, wrists, shoulders, knees, ankles	"Heart normal"	Weight 250 Gm. Adhesive pericarditis. Healed rheumatic endocarditis of mitral valve. Left auricular endocarditis. Petechial epicardial and subendocardial hemorrhages	Bronchopneumonia Congestive failure	Pyelonephritis Renal calculi Terminal skin and visceral hemorrhages	

No.	Sex											
14	M	49	50	50	Acute polyarthritis with residual deformity	Progressive multiple deformity	Wrists, fingers, elbows, knees, spine	Sounds weak "tic-tac" quality Apical systolic murmur B.P. 120/70 ECG—low voltage QRS, high in Leads II and III	Weight 430 Gm. Adhesive pericarditis. Arteriosclerotic thickening of mitral, aortic and tricuspid valves	Lobar pneumonia	Diffuse nephritis	Subcutaneous nodules
15	F	58	61	65	Pain in right shoulder	Insidious, progressive, multiple deformity	Upper and lower extremities, spine	Enlarged heart Sounds fair Harsh apical systolic murmur. B.P. 190/80; 150/74 ECG—L.A.D.	Weight 500 Gm. Adhesive pericarditis	Congestive failure		Hypertension
16	F	12	11½	27	Acute rheumatic fever (joint involvement) at 11½ years of age	Recurrence with cardiac involvement at 11½ years of age with residual joint deformity. Recurrence at 20 and 27 years of age.	Fingers, spine	Enlarged heart M.I., M.S., A.S., A.I. (Predominant) B.P. 190/0 ECG—R.A.D. high voltage P.R. 0.42 sec., intraventricular block	Weight 820 Gm. Focal adhesive pericarditis. Healed rheumatic endocarditis of mitral and aortic valves. Left auricular endocarditis. Aschoff bodies in myocardium	Sudden death		Active rheumatic fever with congestive failure
17	F	17	50	51	Pain and swelling of toes	Progressive, insidious, multiple deformity. Bedridden 16 years	Spine, upper and lower extremities	Enlarged heart Persistent tachycardia Paroxysmal auricular fibrillation B.P. 104/54	Weight 270 Gm. Obliterative pericarditis. Acute interstitial myocarditis	Congestive failure Jaundice Coma	Biliary cirrhosis Adenoma of thyroid	Episcleritis
18	M	46	53	54	"Rheumatism"	Recurrence 3 years later with further deformity—progressive	Upper and lower extremities	Enlarged heart A.I. B.P. 125/45 ECG—R.A.D.	Weight 450 Gm. Healed rheumatic endocarditis of mitral and aortic valves. Left auricular endocarditis	Bronchopneumonia Congestive failure		

TABLE I—Cont'd

AGE	SEX	AGE OF ONSET OF JOINT DEFORMITY (YR.)	AGE HEART DISEASE DISCOVERED (YR.)	AGE AT DEATH (YR.)	JOINT INVOLVEMENT TYPE OF ONSET	JOINT INVOLVEMENT COURSE	JOINT INVOLVEMENT DEFORMITY	HEART INVOLVEMENT CLINICAL	HEART INVOLVEMENT POST MORTEM	CAUSE OF DEATH	OTHER PATHOLOGIC FINDINGS	MISCELLANEOUS
39	M	50	50	50	"Rheumatism" at 12 years of age	Multiple joint pains with progressive deformity	Spine, upper and lower extremities	Enlarged heart M.S., M.I., A.I. B.P. 115/68 ECG—L.A.D., auricular fibrillation	Weight 490 Gm. Recurrent active endocarditis of mitral and aortic valves. Fibrinous pericarditis. Left auricular endocarditis	Congestive failure Lipoid pneumonia		
30	M	19	19	31	Pain in spine with progressive stiffness an convexity	Periodic exacerbations for 4 years with pain in other joints	Spine (predominantly Mario-Strümpell), shoulders, elbows, wrists, fingers, hips, knees	Enlarged heart M.S., M.I., A.S., A.I. B.P. 110/30 ECG—L.A.D. QRS widened paroxysmal auricular fibrillation	Weight 530 Gm. Healed rheumatic endocarditis of mitral, aortic, tricuspid and pulmonic valves. Bacterial vegetative endocarditis mitral valve. Left and right auricular endocarditis. Focal adhesive pericarditis. Seared Aschoff bodies in myocardium	Pulmonary infarction Congestive failure	Splenic infarcts	
27	M	31	33	41	"Rheumatism" at 11 and 17 years of age	Acute polyarthritis at 31 years of age with progressive deformity	Spine, wrists, hands, knees, hips	Enlarged heart M.I., M.S. Pericarditis B.P. 110/64 ECG—R.A.D. Premature ventricular beats	Healed rheumatic mitral endocarditis. Obliterative pericarditis	Bronchopneumonia Congestive failure		Polyglandular syndrome

No.	Sex				Complaint	Course	Joints	Clinical heart findings	Autopsy findings	Cause of death	Remarks	
22	F	59	64		Multiple joint pains	Progressive deformity. Bedridden 3 years	Spine (marked), upper and lower extremities	No cardiac enlargement M.I.	Weight 150 Gm. Fibrinous pericarditis. Brown atrophy of heart. Calcification base of mitral, aortic, and tricuspid valves	Bronchopneumonia Congestive failure		
23	F	31	40		Pain in left knee with deformity	Two years later progressive, multiple deformity	Hands, wrists, knees, hips, ankles, spine	"No heart disease"	Weight 230 Gm. Healed rheumatic mitral endocarditis. Pedunculated, hyalinized nodule mitral valve	Bronchopneumonia Congestive failure		
24	M	27	36	40	Stiffness in back. Acute arthritis at 35 years of age	Progressive multiple deformity	Spine (marked), upper and lower extremities	Enlarged heart A.I. B.P. 130/60	Weight 800 Gm. Healed rheumatic endocarditis of aortic valve. Healed Aschoff bodies in myocardium	Congestive failure Bronchopneumonia		
25	F		75			Progressive deformity	Wrists, hands, elbows, hips, knees	No cardiac diagnosis B.P. 140/70 ECG—L.A.D.	Weight 300 Gm. Acute fibrinous pericarditis	Pericarditis Congestive failure Bronchopneumonia		
26	F	57	72	73	Pain and deformity, knees	Progressive, insidious, multiple deformity	Spine (marked), upper and lower extremities	Enlarged heart A.S., M.I.	Weight 300 Gm. Healed rheumatic mitral and aortic endocarditis. Left auricular endocarditis	Uremia	Partial necropsy (heart only)	
27	M	50	70	70	Acute polyarthritis	Frequent recurrences with progressive deformity	Wrists, fingers, knees	Enlarged heart Syphilitic aortitis B.P. 105/58	Weight 500 Gm. Healed rheumatic mitral, aortic, and tricuspid endocarditis. Adherent pericardium. Syphilitic aortitis	Congestive failure	Cirrhosis of liver	Wassermann 4+

TABLE I—CONT'D

CASE	SEX	AGE OF ONSET OF JOINT DEFORMITY (YR.)	AGE JOINT DISEASE DISCOVERED (YR.)	AGE AT DEATH (YR.)	JOINT INVOLVEMENT			HEART INVOLVEMENT		CAUSE OF DEATH	OTHER PATHOLOGIC FINDINGS	MISCELLANEOUS
					TYPE OF ONSET	COURSE	DEFORMITY	CLINICAL	POST MORTEM			
	F	42		64	Acute polyarthritis	Frequent recurrences with progressive deformity	Wrists, fingers, shoulders, ankles, knees	Enlarged heart B.P. 230/104 ECG—marked L.A.D. Hypertensive heart disease	Weight 370 Gm. Healed rheumatic mitral, aortic, and tricuspid endocarditis with calcification at bases	Pulmonary infarct		Hypertension at 53 years of age Acute arthritis on admission
	F	25	26	28	Stiffness of knees, hands, hips	Progressive deformity	Spine (marked), upper and lower extremities	Enlarged heart M.I.	Weight 320 Gm. Active rheumatic mitral endocarditis. Left auricular endocarditis. Adhesive pericarditis, Pericardial effusion (400 c.c.)	Streptococcal meningitis Pituitary abscess Bronchopneumonia Congestive failure		
30	F	39	63	64	"Rheumatism" of arms. Backache	Progressive, insidious deformity	Elbows, shoulders, hips, knees	Enlarged heart M.I., A.S. B.P. 130/68	Weight 230 Gm. Healed rheumatic mitral and aortic endocarditis. Calcification base of aortic valve. Left auricular endocarditis	Retroperitoneal sarcoma	Thrombosis of inferior vena cava Amyloidosis of liver	Hypertension at 60 years of age

31	F	43		60	Acute polyarthritis	Progressive, insidious, multiple deformity	Spine (marked), shoulders, wrists, fingers, knees, ankles	? enlarged heart B.P. 138/64; 180/108 ECG—L.A.D.	Weight 260 Gm. Healed rheumatic endocarditis of mitral, aortic and tricuspid valves. Calcification mitral ring; aortic leaflets. Indeterminate vegetations aortic valve	Congestive failure	Right knee joint-cavity distended with thick yellow gelatinous fluid, marked thickening of synovium; new bone formation
32		54	55	60	Multiple joint pains	Progressive deformity	Upper and lower extremities	Enlarged heart A.S. (?) B.P. 180/100 ECG—L.A.D.	Weight 700 Gm. Healed rheumatic endocarditis of mitral and aortic valves. Calcification base of aortic valve. Indeterminate endocarditis aortic valve	Broncho-pneumonia Congestive failure	
33	M	30		53	Pain in the neck	Episodes of acute polyarthritis	Upper and lower extremities, cervical spine	No clinical evidence of heart disease B.P. 108/78 ECG—normal	Weight 420 Gm. Healed rheumatic endocarditis of aortic and mitral valves. Fibrinous pericarditis	Broncho-pneumonia Congestive failure	Subcutaneous nodles

Key to abbreviations used in table:

M.I. = Mitral insufficiency.

M.S. = Mitral stenosis.

A.I. = Aortic insufficiency.

A.S. = Aortic stenosis.

L.A.D. = Left axis deviation.

R.A.D. = Right axis deviation.

thirty-three of these cases there were cardiac lesions which were not the result of hypertension or coronary artery disease.

Although doubt has been cast on the accuracy of the separation into rheumatoid (atrophic, chronic infectious, proliferative) and osteo-arthritis (hypertrophic, senile, degenerative), the cases presented in this study were chosen in accordance with the classification of "rheumatoid arthritis" based on clinical, laboratory, and radiographic observations as defined by the American Rheumatism Association.[22] Doubtful cases of isolated hip, knee, or shoulder involvement, hypertrophic changes in the spine, and those with Heberden's nodes were eliminated, as were those with a specific cause, such as tuberculosis, syphilis, gonorrhea, pyogenic infection, gout, and central nervous system disease. All patients included in this material suffered from an inflammatory poly-articular process which was progressive in character and resulted in deformity and disability. These patients were closely followed in the hospital and in the pavilion for the disabled for months to years (twenty-six years in Case 1) before death occurred. The roentgenograms were characteristic of this disease in the earlier stages, but with advancing years, additional hypertrophic degenerative changes were noted. In many cases there was anatomic verification of the nature of the joint disease.

Gross and histologic study was made in all cases. Cardiac lesions designated as rheumatic were usually apparent from the gross appearance alone. The criteria employed were thickening of the edges of the mitral and tricuspid leaflets, plus thickening and shortening of their chordae tendineae, thickening and rolling of the free edges of the aortic leaflets, frequently with commissural adhesions, and thickening and occasionally calcification of the auricular endocardium (MacCallum lesions). Young Aschoff bodies were found in one case only. The microscopic appearance was characteristic. The diagnosis of acute rheumatic pericarditis was made when there was the typical "bread and butter" exudate grossly, and, microscopically, when palisading of fibroblasts and occasional round cells were seen. The lesions designated as nonspecific failed to show either sufficiently or clearly the characteristic rheumatic stigmata.

RESULTS

A detailed analysis of the results of this study is presented in Tables I and II. There were thirty-eight cases of chronic rheumatoid arthritis in adults in which necropsy was performed. Of this number, thirty-three presented cardiac lesions which were not the result of arteriosclerosis or hypertension. Of this group, twenty-four had rheumatic valvular disease, ten with pericarditis and fourteen without. The localization of valvular involvement is shown in Table III. Healed rheumatic valvulitis was present in twenty-three cases, recurrent rheumatic endocarditis of the mitral and aortic valves in two cases, and early active

TABLE II

CLINICAL AND NECROPSY DATA ON FIVE CASES OF RHEUMATOID ARTHRITIS WITHOUT RHEUMATIC HEART DISEASE

CASE	SEX	AGE AT ONSET OF JOINT DEFORMITY (YR.)	AGE AT DEATH (YR.)	TYPE OF ONSET	COURSE	DEFORMITY	POST MORTEM
1	F	35	54	Pain in toes	Acute exacerbations with progressive deformity	Upper and lower extremities, spine	Hypertensive heart disease. Arteriosclerosis of aorta and coronary arteries. Pulmonary edema
2	F	41	50	Pain in toes	Insidious, progressive	Upper and lower extremities	Old and recent coronary occlusion with posterior myocardial infarction
3	F	50	57		Insidious, progressive; bedridden past six years	Upper and lower extremities	Perivascular sarcoma of cerebrum
4	M	35	44	Pain in neck and lower back	Insidious, progressive	Marie-Strümpell spine; knees, shoulders, ankles	Intussusception of jejunum into stomach with hemorrhagic infarction and early gangrene of jejunum
5	M	57	66	Pain in arms	Insidious, progressive	Shoulders, knees, hands; marked periarthritis	Postoperative hemorrhage from a branch of the gastroduodenal artery. Old multiple coronary occlusions

TABLE III

ANATOMIC LOCALIZATION OF RHEUMATIC VALVULITIS IN TWENTY-FOUR CASES

	MITRAL	AORTIC	MITRAL AND AORTIC	MITRAL, AORTIC, AND TRICUSPID	MITRAL, AORTIC, TRICUSPID, AND PULMONIC	TOTAL
Cases without pericarditis	3	3	6	2	0	14
Cases with pericarditis	3	0	3	3	1	10
Total	6	3	9	5	1	24

rheumatic mitral valvulitis in one case. Superimposed, indeterminate, vegetative or terminal endocarditis was found in four cases, and superimposed nodular calcification of the leaflets or bases of the valves was noted in seven. Of these, except for one patient who was 48 years of age, all were 60 years or more at the time of death. A superimposed bacterial endocarditis was present in one case. This was not suspected clinically, but, on section, numerous clumps of cocci were demonstrated on the mitral valve. In one case syphilitic aortitis was also present.

There were nine cases of pericarditis without associated valvular lesions. In this group there were one case of acute rheumatic pericarditis, two of acute fibrinous but nonspecific pericarditis, and six of adherent or obliterative pericarditis. Of the ten cases of combined valvulitis and pericarditis, acute rheumatic pericarditis was present in three. In the remaining seven cases there were areas of focal adhesive pericarditis or "milk spots." Pericardial effusion (400 c.c.) was present in only one case, and was apparently due to congestive failure.

In the cases of rheumatic valvular disease, the heart weights ranged from 220 to 820 grams; the mean weight was 400 grams, which is greater than the accepted normal. Aschoff bodies in the myocardium were noted in only one case; here they were the only evidence of an active rheumatic process. Myocardial lesions which were regarded as healed Aschoff bodies were found in two cases. In many cases there were small areas of perivascular scarring, but the specificity of the lesion could not be demonstrated. Acute interstitial myocarditis was present in one case.

CLINICAL CONSIDERATIONS

There were 14 male and 19 female patients in this series. Congestive heart failure occurred in 22 cases, and was either the cause of death or preceded a terminal bronchopneumonia in these cases. As can be seen in Table IV, the majority lived beyond the usual life expectancy of patients with rheumatic heart disease. This is undoubtedly a result of the inactivity imposed upon such patients by the chronic arthritis; most of them had been completely bedridden for many years. Since the period of hospitalization was extremely long for all patients, each was examined frequently by many observers. Despite this, the clinical diag-

TABLE IV

AGE AT DEATH IN THIRTY-THREE CASES

AGE IN YEARS	20 TO 25	26 TO 30	31 TO 35	36 TO 40	41 TO 45	46 TO 50	51 TO 55	56 TO 60	61 TO 65	66 TO 70	71 TO 75
Number of cases	1	2	2	3	1	6	5	4	5	2	2

TABLE V

CASES WITH VALVULAR DISEASE IN WHICH THE CLINICAL DIAGNOSIS WAS NOT MADE

CASE NO.	ANATOMIC DIAGNOSIS	CLINICAL DIAGNOSIS
13	Mitral insufficiency	"Heart normal"
22	Mitral stenosis and insufficiency	"No heart disease"
27	Mitral, aortic, and tricuspid insufficiency. Syphilitic aortitis	Syphilitic aortitis
28	Mitral, aortic, and tricuspid insufficiency	Hypertensive heart disease
31	Mitral and tricuspid insufficiency. Aortic stenosis	? Enlarged heart
33	Mitral and aortic insufficiency	"No heart disease"

posis of rheumatic heart disease was not made in 14 of the 32 cases (in one case there was no note concerning the heart). Of these 14 cases, the presence of obliterative or adhesive pericarditis was not suspected in 6; acute fibrinous pericarditis was not suspected in 2. The diagnosis of rheumatic valvular disease was not made in 6 cases. The anatomic lesions are shown in Table V. In the case of syphilis, apparently the

Fig. 1.—Case 11 (C. B.). *A*, Marked arthritis deformans. Premature senility. *B*, Typical advanced deformity of hand, with characteristic atrophic radiographic changes. *C*, Electrocardiogram shows 2:1 auricular flutter and left axis deviation.

signs of aortitis overshadowed the murmurs of rheumatic valvular disease. Frequently a complete, anatomic, valvular diagnosis was not made clinically, but in all such cases the presence of rheumatic heart disease was clearly recognized.

Fig. 2.—Case 13 (M. V.). A, Deforming, anklyosing arthritis, cachexia and cutaneous hemorrhages. B and C, Marked decalcification of bones, with narrowing of the joint clefts and broadening of the bases of the proximal phalanges.

In view of the opinion of many that patients with rheumatoid arthritis who exhibit evidence of cardiac involvement have, or have had, rheumatic fever, the clinical course of each of the thirty-three patients was closely studied. Only three (Cases 11, 16, and 20) gave a history of frank rheumatic fever earlier in life. One had an attack of joint and cardiac involvement at the age of 8 years, with frequent recurrences

Fig. 3.—Case 19 (A. B.). *A,* Marked arthritis deformans; cachexia. *B,* Left ventricular enlargement, with straightening of upper left cardiac contour; right hydrothorax. *C,* (1) Electrocardiogram Aug. 15, 1934, shows regular sinus rhythm with broadened, notched P waves, (2) Aug. 23, 1934, auricular fibrillation present.

in childhood, but did not develop multiple joint deformities with an insidious, progressive course until the age of 44 years. The second patient had an initial attack of rheumatic fever in childhood; a recurrence six months later was followed by residual deformity. The third patient suffered from chronic active rheumatic fever for four years,

during the course of which the joints became deformed. Two patients (Cases 19 and 21) probably had rheumatic fever in childhood, although whether they had cardiac involvement at that time could not be ascertained from the history. One developed insidious, progressive deformities at the age of 50 years, the other, progressive deformity after an acute polyarthritis at the age of 31 years.

Of the remaining twenty-eight cases, in fourteen the joint deformities occurred insidiously and were progressive, and there were no attacks of acute polyarthritis. This is the so-called "primary chronic polyarthritis" of the German authors.[1, 2, 4] In an equal number, there was an attack of acute polyarthritis at the onset of the illness, followed by progressive deformity, or frequent exacerbations of acute arthritis occurred during the course of the disease ("secondary chronic polyarthritis"). The cardiac involvement in both groups was comparable in both type and extent of endocardial and pericardial involvement (Table VI). Of the five cases without cardiac involvement (Table II), the course was insidious and progressive in four. Of great interest in regard to the etiological relationship between joint and cardiac involvement is Case 9; this patient, with marked joint deformity for seven years, after repeated attacks of acute polyarthritis, was admitted to the hospital because of acute rheumatic fever. Necropsy revealed acute rheumatic pericarditis with no evidence of previous cardiac involvement.

TABLE VI

COMPARISON OF CARDIAC INVOLVEMENT IN CASES OF INSIDIOUS PROGRESSIVE
DEFORMITY AND CASES WITH ACUTE ATTACKS OF POLYARTHRITIS

CARDIAC INVOLVEMENT	INSIDIOUS PROGRESSIVE ("PRIMARY CHRONIC POLYARTHRITIS")	ACUTE POLYARTHRITIS ("SECONDARY CHRONIC POLYARTHRITIS")
Pericarditis	5	4
Valvulitis	8	6
Valvulitis and pericarditis	1	4
Total	14	14

The temporal relation between the age at which joint deformity occurred and the age at which heart disease was first discovered could be reasonably ascertained in 18 cases. Fifteen cases were eliminated either because the cardiac involvement was not recognized clinically or the history was inadequate. Of the remaining cases, in 14 joint deformity occurred from one to eighteen years (average, eight years) before the discovery of heart disease. In 2 cases cardiac involvement preceded the rheumatoid arthritis. Cardiac and joint involvements were discovered concomitantly in 2 cases.

Although it would appear from this that, in the majority of instances, cardiac involvement followed a prolonged period or repeated attacks of joint involvement, this cannot be stated with assurance, for the adequacy of the initial cardiac examination is questionable. Baggenstoss

and Rosenberg[23] have expressed the opinion that the initial, although mild and slowly progressive, course of joint involvement may cause minimal cardiac damage which is not great enough to be recognized clinically. It must be remembered, however, that the arthritic constantly seeks medical care, and that each of these patients had been examined by

A.   C.

B.   D.

Fig. 4.—Case 20 (H. H.). *A*, Typical Marie-Strümpell spine. Arthritis of hands is also noted. *B*, The electrocardiogram shows auricular fibrillation and left axis deviation. *C*, Mitral stenosis and insufficiency. Dilatation of left auricle. *D*, Rheumatic endocarditis of aortic valve. Hypertrophy of left ventricle.

competent physicians in many clinics and hospitals, and that their records, particularly those of the Montefiore Hospital admissions, were unusually thorough.
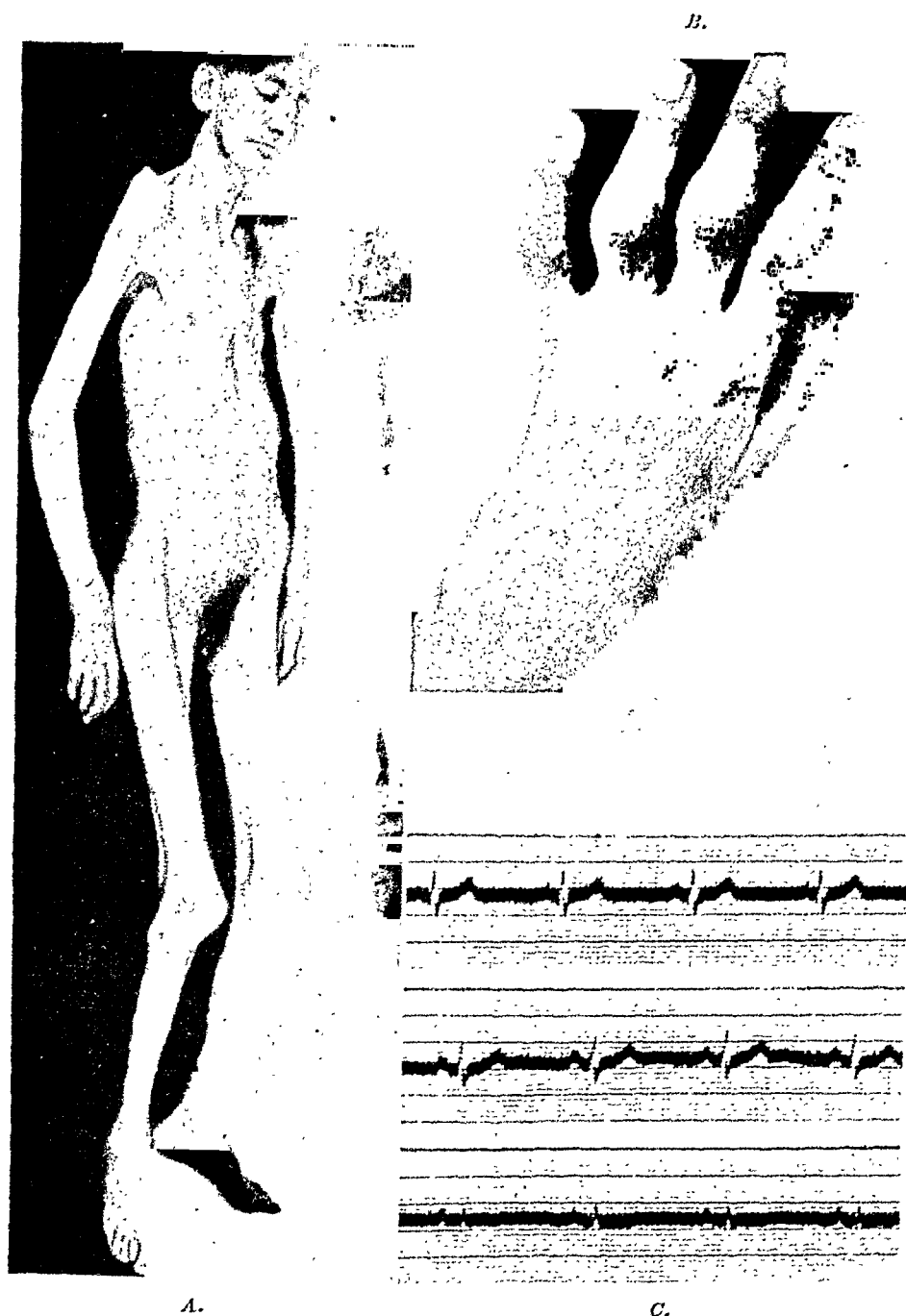
Fig. 5.—Case 21 (H. G.). *A*, *Marked arthritis deformans. Infantile gigantism.* B. *Typical fusiform swelling of proximal interphalangeal joints in rheumatoid arthritis. C, Electrocardiogram shows regular sinus rhythm with tendency to right axis deviation.*

DISCUSSION

The paucity of adequate, complete clinicopathologic studies in the American literature has led to arbitrary separation of rheumatoid

arthritis as an entity separate and distinct from rheumatic fever and rheumatic heart disease, despite the histologic similarity of the joint changes and the identity of the subcutaneous nodules (until Collins'[25] and Bennett, Zeller, and Bauer's[26] recent papers). From the earlier studies it is not difficult to understand why such concepts came into being, for the conclusions were always based on the clinical recognition of cardiac involvement in cases of chronic arthritis. The inaccuracy of clinical recognition has already been mentioned.

Thus, McCrae,[27] among five hundred cases, found pericarditis in six and definite valvular disease in forty (8 per cent), in one quarter of which the cause may have been arteriosclerosis. Of eighty cases of arthritis deformans reported by Boas and Rifkin,[28] in fourteen (17.5 per cent) there was valvular disease clinically. Wetherby[29] reported seven cases of rheumatic heart disease (2 per cent) out of 350 cases of chronic arthritis. Monroe[30] reports an incidence of 4 per cent. Master and Jaffe,[31] judging from normal electrocardiographic observations, concluded that rheumatoid arthritis is not associated with heart disease. Dawson and Tyson[32] found a 7 per cent clinical incidence, and Bayles and McGinn[33] reported 5 per cent in one hundred consecutive rheumatoid arthritic patients. Pemberton[34] admits that there may be more in common between acute rheumatic fever and chronic arthritis than has hitherto been accepted, but concludes that they are distinct clinical entities with similar manifestations. In European countries such studies have been more frequent, and there the reported incidence ranges from Coates'[10] report of 4 per cent to Kahlmeter's[17] 40 per cent.

Probably the first description of a case of deforming arthritis with associated cardiac lesions was given by Todd,[35] in 1843. Three years later Romberg[36] described a similar case. However, it was not until 1881 that Charcot,[13] as the result of pathologic observations on a larger series of such cases, concluded that "these are not two fundamentally distinct diseases, but two manifestations of one and the same diathetic state." The results of other pathologic studies since that time indicate a rather more than fortuitous association (Table VII). In Baggenstoss and Rosenberg's[23] series the incidence of rheumatic heart disease was 56 per cent. Clawson[37] and his associates have found some form of rheumatic heart disease in 33 per cent of all cases of rheumatoid arthritis, and Bayles,[24] in 22 per cent.

In our study, 25 of 38 patients showed definite rheumatic heart disease at necropsy (65.7 per cent), and 8 others showed cardiac involvement of a nonspecific infectious nature. This percentage is rather high and, because the number of cases is not large, undoubtedly does not represent an accurate estimate of the true incidence. Nevertheless, the addition of our data to those in the literature affords a reasonable basis for concluding that an extremely close relationship exists between rheumatic fever and rheumatoid arthritis.

TABLE VII

POST-MORTEM STUDIES OF THE HEART IN CHRONIC ARTHRITIS

AUTHOR	YEAR	TYPE OF ARTHRITIS	NUMBER OF CASES				
			ARTHRITIS	ENDO-CARDITIS	PERI-CARDITIS	PERI-CARDITIS AND ENDO-CARDITIS	TOTAL WITH CARDIAC INVOLVEMENT
Charcot	1881	"Chronic rheumatism"	9		4		4
Kast	1901	"Primary chronic arthritis"	13	2	2		4
		"Secondary chronic arthritis"	4	2		1	3
Pribram	1902	"Primary chronic arthritis"	9		2		2
		"Secondary chronic arthritis"	4	2		1	3
Grzimek	1932	"Genuine arthritis deformans"	91	39			39
Klinge	1933	Chronic polyarthritis	10	6	1	1	8
		"Rheumatismus nodosus" of spine	1	1			1
Baggenstoss and Rosenberg	1941	Chronic infectious (rheumatoid) arthritis	25	8	4	4	16
Bayles	1942	Rheumatoid arthritis	23	4	0	2	6
Young and Schwedel	1943	Chronic rheumatoid arthritis	38	14	9	10	33

Our observations in regard to the severity of the cardiac lesions in rheumatoid arthritis are not in agreement with those of Baggenstoss and Rosenberg,[23] who found that cardiac lesions were more widespread in the hearts of patients with rheumatic fever than in the hearts of those with rheumatoid arthritis. Quantitatively, as well as qualitatively, there was no essential difference between the severity or extent of the cardiac lesions in rheumatoid arthritis and those associated with rheumatic fever. We cannot agree, either with these same authors when, because they found histologic evidence of rheumatic activity in 10 of the 14 cases, they concluded that, if a rheumatic lesion is clinically apparent, the chances are great that the process is still active. In only 6 of our 19 cases of rheumatic heart disease in which the diagnosis was made clinically were there pathologic stigmata of rheumatic activity.

Despite the severity of the cardiac lesions, however, it is quite apparent that they played a comparatively minor role in the clinical picture except as a late manifestation, and also as a mode of death. Cardiac symptoms were relatively unimportant or were nonexistent

throughout the major part of the lives of these patients. It was not the heart disease, but the joint disease, for which they first sought medical attention. Eventually, however, congestive failure supervened in the majority of cases, but, as has been previously mentioned, at a much later age than is usual in patients with rheumatic heart disease without rheumatoid arthritis. The restricted life imposed on such patients because of their joint deformities probably is responsible for the degree of longevity achieved.

Kast[1] and Pribram[2] differentiated "primary" from "secondary" chronic polyarthritis, stating that, in the former, cardiac involvement was less frequent and usually played an unimportant role if present. In the secondary form, they found that the cardiac involvement was quite often marked, and might dominate the entire clinical picture. Barjon,[16] however, found that the incidence of heart disease was 21 per cent in the former, and 20.5 per cent in the latter, type. Judging from his sixty-two cases and other reports[11, 12, 14, 15] in the French literature, he concluded that no difference existed. Our observations are in agreement in this respect.

The fact that a history of frank rheumatic fever was obtained in only three cases fails to support the concept that, in those cases of rheumatoid arthritis in which heart disease is also found, rheumatic fever had at one time been present. It must be admitted, however, that the absence of such a history is not necessarily too significant. In view of the frequency of the cardiac lesions, however, this point is, at best, of little practical significance, and resolves itself into one of nomenclature rather than etiology. No fundamental purpose is served by separating the two rheumatic diseases, and the issue would be clarified by grouping both under the term "rheumatic state," especially since the cause is unknown in both. It is well known that rheumatic fever is protean in its manifestations and in its course. The addition of the "rheumatoid" cardiac manifestations thus adds to, rather than detracts from, such a concept.

It is interesting to speculate upon the varied vulnerability of the heart and joints, and upon the apparent reciprocal relationship. When one structure is greatly involved, the other is relatively, or absolutely, spared. This variability of tissue response to the same noxious agent has been observed in various disease states. In rheumatic fever, Gross[38] has ascribed the low incidence of valvular involvement in older people to the regressive changes in the musculature and vessels of the valves, resulting in a comparative avascularity. Whether this explanation is purely morphologic, or whether it depends on an as yet unexplained immunologic response, is still to be ascertained.

SUMARY AND CONCLUSIONS

A post-mortem study of 38 cases of chronic rheumatoid arthritis revealed cardiac lesions in 33, in 25 of which (65.7 per cent) the process

was considered to be rheumatic in origin, and of a nonspecific infectious nature in the remaining 8. An active rheumatic process was present in only 6 cases. A history of rheumatic fever was obtained in only 3 cases, and of probable rheumatic fever in 2 others. In 18 patients the arthritis was insidious and progressive, and, in 15, acute attacks of polyarthritis occurred during the course of the disease. The extremely high incidence of rheumatic heart disease in rheumatoid arthritis which was found in this and previous pathologic studies suggests an extremely close relationship which should lead to consideration of the possibility that they may be manifestations of the same underlying disease process.

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COARCTATION OF THE AORTA: CLINICAL AND ROENTGENOLOGIC ANALYSIS OF THIRTEEN CASES

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COARCTATION of the aorta is a congenital anomaly which presents interesting clinical and radiological diagnostic features. The developmental anatomy has been well described many times, particularly by Abbott,[1] and any repetition would be superfluous. It is divided into two types, namely, the infantile type, which occurs in children up to the age of 1 year, and the adult type. It is with the latter type that we are concerned.

The incidence of the condition has been estimated to be 1 in 1,500 cases by Blackford,[2] who based his figures on a series of 68,300 routine autopsy reports. Evans[3] found 26 cases of coarctation of the aorta in 19,217 routine necropsies at the Baron Institute of Pathology, London. This included both the infantile and the adult type. There were 11 cases of coarctation of the adult type in 16,215, or an incidence of 1 in 1,471. Levine[4] estimates that 0.1 per cent of the entire population have this anomaly.

The incidence of coarctation in our series was much lower, i.e., approximately 1:10,000. This was in a series of routine physical examinations for army service upon an unselected group of men between the ages of 18 and 35 years. A number of the men were over 35 years, but the percentage of these was so small as to be almost negligible.

Why there is such a great discrepancy between the number of cases noted in routine necropsy reports and the number diagnosed on routine physical examination is difficult to explain. The pathologist can include in his series cases of slight narrowing of the aorta at the site of the ductus arteriosus. In such cases there are no physical signs, and radiological examination shows nothing abnormal. An example may be found in the report by Hallock and Hebbel[5] of the nonclinical type of coarctation. Their patient had no hypertension. The diagnosis was made from the cardiac examination only, and, on autopsy, a slight constriction of the aorta at the point of attachment of the ductus arteriosus was found. In addition to this nonclinical group of cases, there have undoubtedly been some in which the diagnosis was not made. King[6] commented on the fact that only one case of coarctation of the aorta was diagnosed from the time of the founding of the Johns Hopkins Hospital to 1923. In discussing a series of eight cases in which the diagnosis was made clinically, Lewis[7] commented on the number of times some of the patients were examined before the correct

diagnosis of coarctation of the aorta was made. The majority of the cases which he reported were in men who were examined and pronounced fit for active service in World War I, and showed no symptoms of cardiac disease for some years after their discharge from the British Army.

CASE REPORTS

CASE 1.—The patient, a 28-year-old white man, with no previous knowledge of heart disease, had indulged moderately in athletic activities.
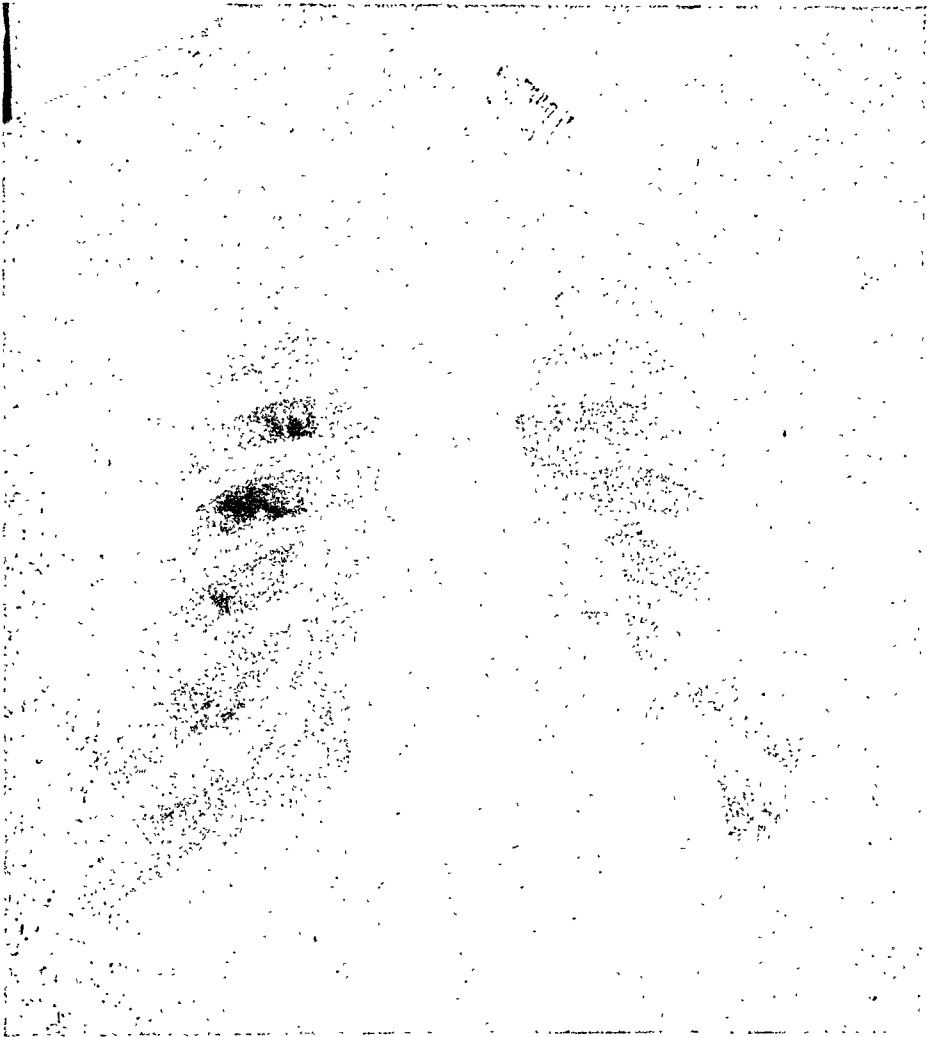
Fig. 1.—Case 1.

Examination revealed a well-developed and well-nourished young man without cyanosis or marked flushing of the face. Carotid pulsations were evident, but not marked. The heart was not grossly enlarged; the apex beat was within the left midclavicular line. Auscultation revealed a harsh, loud, blowing diastolic murmur over the aortic valve and Erb's point. The blood pressure was 200/40. The abdominal aortic and femoral artery pulsations were absent. The blood pressure was not obtainable in the popliteal region. The intercostal vessel pulsations were slight, i.e., they were obtainable only upon extreme pressure on the inferior margins of the ribs.

CASE 2.—The patient was a 21-year-old white man, with no previous knowledge of heart disease. He had led the normal life of a boy and young man and had participated in various types of athletics, but never strenuously.

Examination revealed a well-developed and well-nourished young man. His complexion was normal. The carotid artery pulsations were absent.
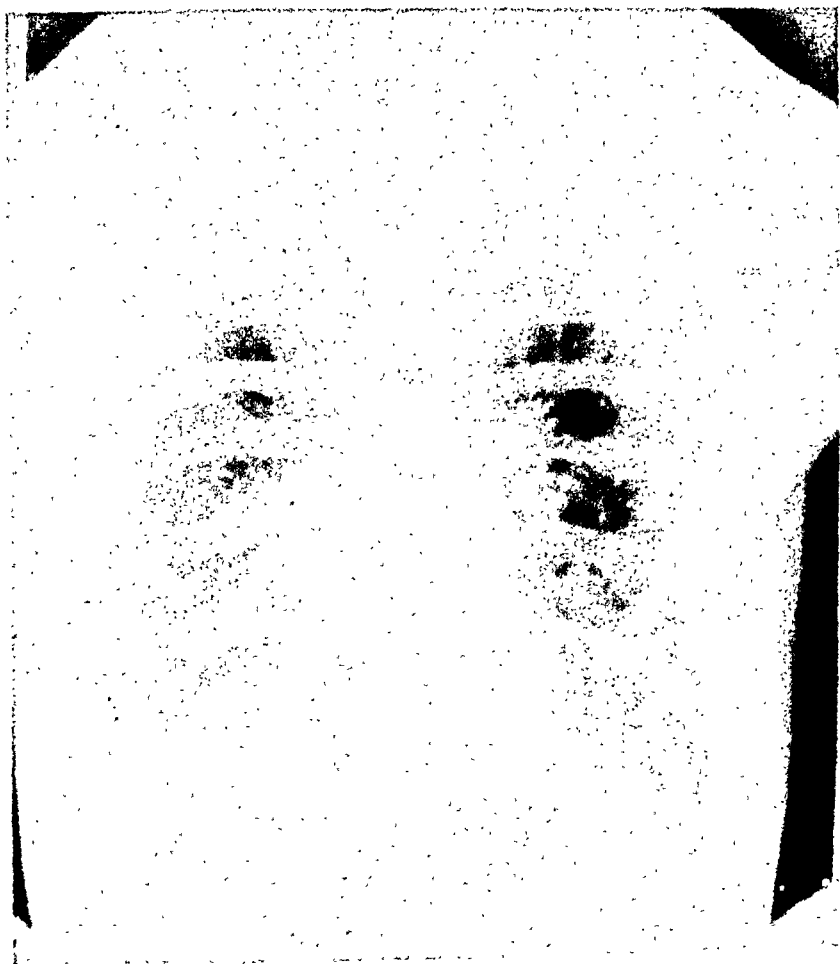
Fig. 2.—Case 2.

The apex beat of the heart was well within the left midclavicular line at the fifth intercostal space. A loud diastolic murmur was heard over the entire precordium; it was most intense at the base of the heart. The blood pressure was 188/88. Abdominal aortic pulsations and femoral artery pulsations were not obtainable. The intercostal vessels were dilated and easily palpable, and, in the right interscapular region, a large vessel was found.

CASE 3.—The patient was a 21-year-old white man who had never been aware of heart disease. No history of athletic endeavor was obtained.

Examination revealed a fairly well-developed, slightly emaciated, young man. His face was of normal color. No carotid pulsation was noted. The cardiac apex was within the left midclavicular line in the fifth intercostal space. Auscultation revealed no murmur, but merely an accentuation of the aortic tones. The blood pressure was 180/110.
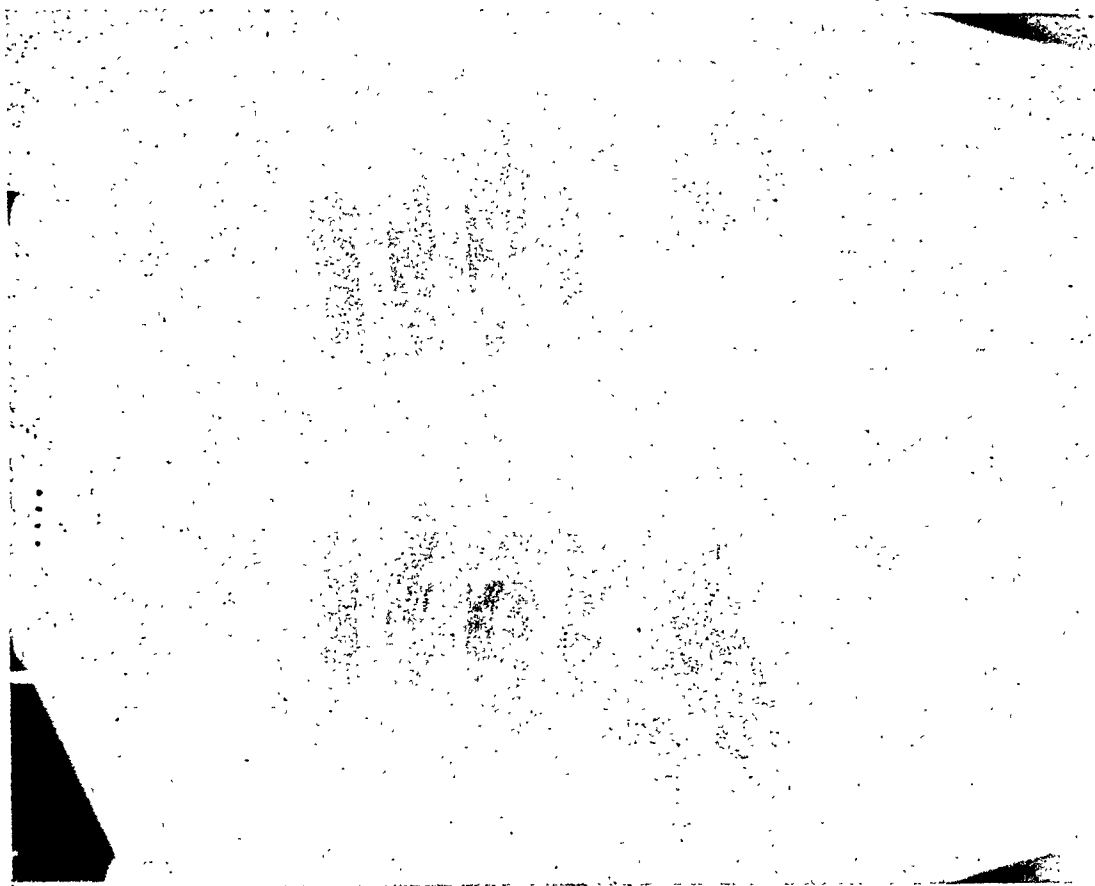
Fig. 4.—Case 4.
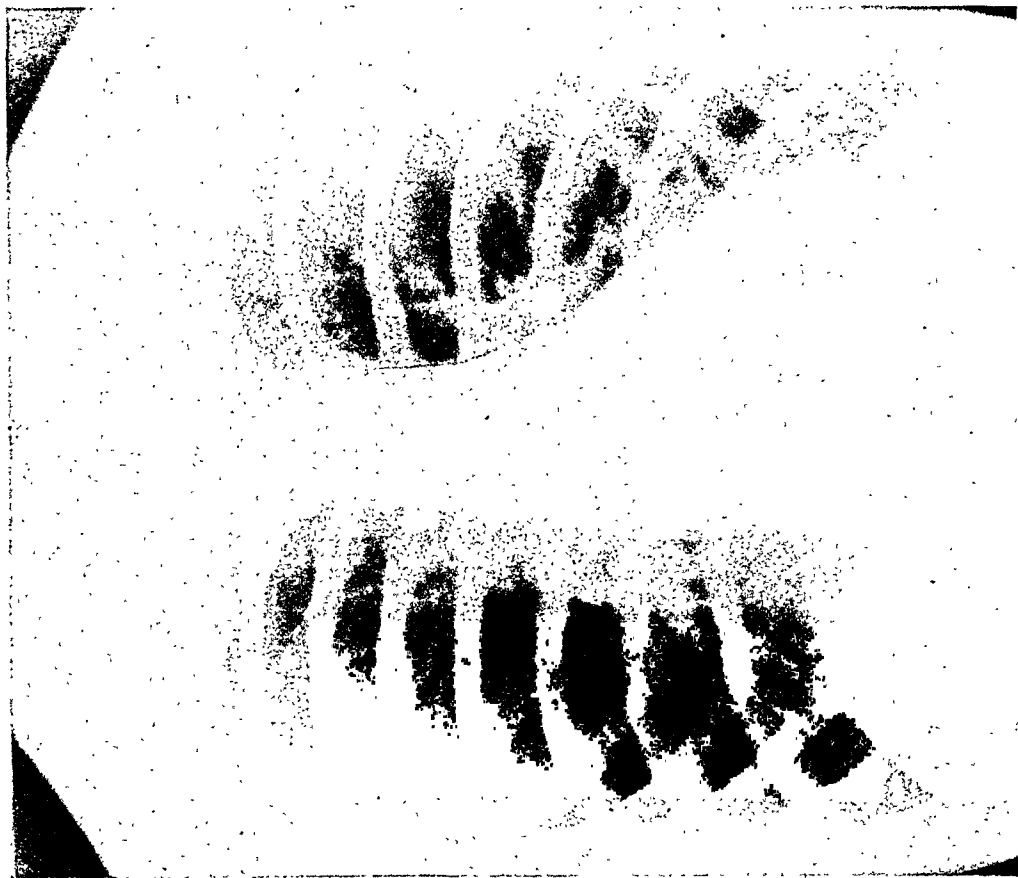
Fig. 3.—Case 3.

Slight pulsation of the abdominal aorta and the femoral arteries was observed. The blood pressure in the popliteal area was 110/80. Moderately strong pulsations of the intercostal vessels were palpated.

CASE 4.—The patient was a 19-year-old white man from whom no previous history of heart disease was elicited. No recreational history was obtained.

Examination revealed a moderately well-developed young man. No abnormal color of the face was noted. The carotid pulsations were marked. The apex of the heart was well within the left midclavicular line at the fifth intercostal space. No cardiac murmurs were heard. The blood pressure was 210-80. The femoral artery pulsations were entirely absent. The blood pressure in the popliteal area was 80/40. Marked pulsations of the intercostal blood vessels were noted.
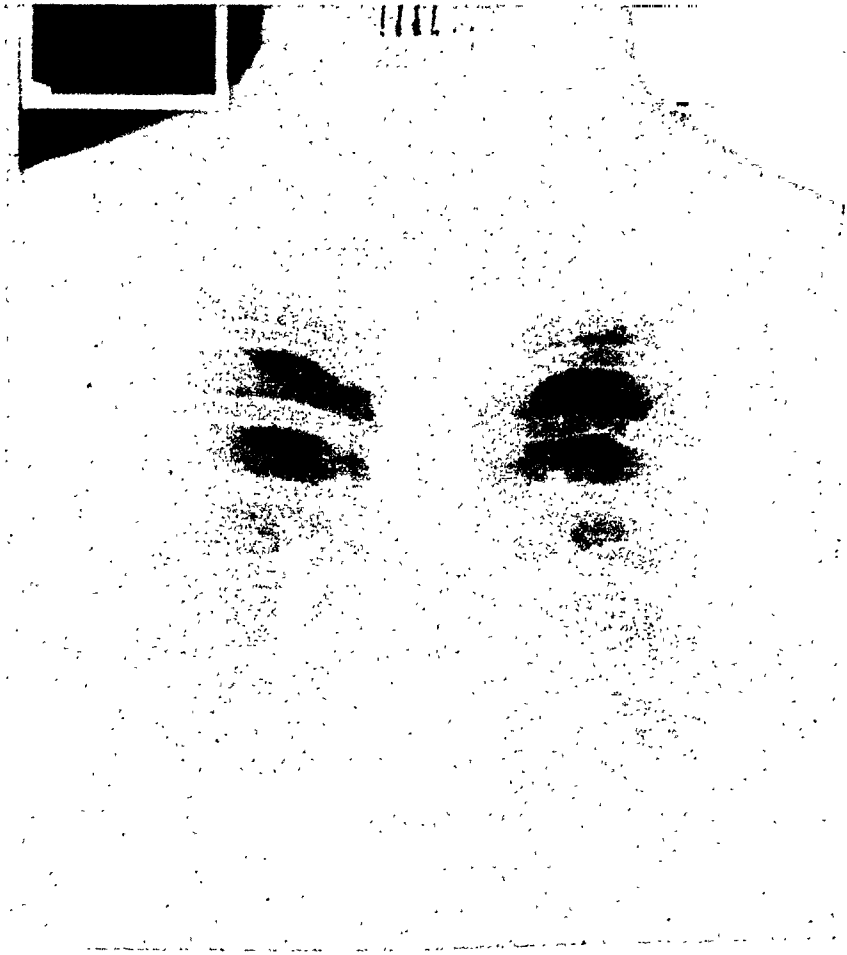
Fig. 5.—Case 5.

CASE 5.—The patient was a 22-year-old white man who had been aware that he had some heart trouble since the age of 14 years. Despite this knowledge, he had played high school and semiprofessional basketball, and had run in the 440-yard dash on his high school track team.

Examination revealed a small, well-built young man. There were marked pulsations of the carotid arteries. The cardiac apex was within normal limits. Auscultation of the heart revealed a loud, blowing, diastolic murmur at the aortic valve and at Erb's point. The blood pressure

was 210/90. Femoral artery pulsations were not obtainable. The blood pressure in the popliteal area was 130/80. Moderate pulsations of the intercostal blood vessels were palpated. The electrocardiogram was normal.

CASE 6.—The patient was a 21-year-old white man who had known that he had a cardiac lesion since early childhood. Five years before the present examination he was told he had high blood pressure. Because of this he had not engaged in any strenuous activities, but felt no discomfort on ordinary activity.

Fig. 6.—Case 6.

Examination revealed a well-developed young white man. The carotid artery pulsation was slight. The heart was not enlarged to physical examination. A soft systolic murmur was heard over the entire precordium, and a low-pitched, diastolic murmur was heard at the aortic valve and at Erb's point. The blood pressure was 170/70. The femoral artery pulsations were not obtainable. The blood pressure in the popliteal area could not be measured. The intercostal blood vessels were palpable upon moderate pressure on the inferior surfaces of the ribs. The electrocardiogram was normal.

CASE 7.—The patient was a 20-year-old white man with no previous knowledge of any cardiac lesion; he gave a history of moderate indulgence in athletic activities.

Examination revealed a well-developed young man. There were moderate pulsations of the carotid arteries. The cardiac apex was 2 cm. to the left of the midclavicular line in the fifth left intercostal space. A loud, blowing, diastolic murmur was heard over the aortic valve and Erb's point. The blood pressure was 220/90. Palpation of the femoral arteries revealed no pulsations, and the blood pressure in the popliteal area could not be obtained. The intercostal vessels were easily palpated, and gave a strong impulse which coincided with cardiac systole.
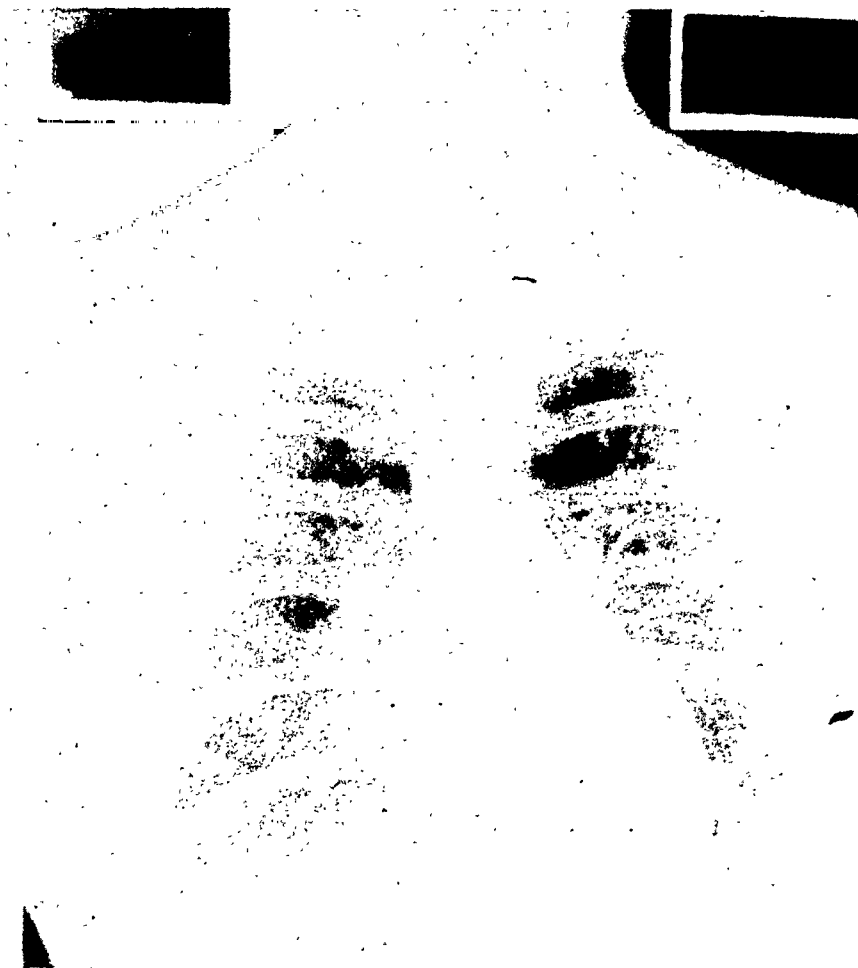
Fig. 7.—Case 7.

CASE 8.—The patient was a 20-year-old white man who had known since the age of 11 years that his blood pressure was elevated. His activity had been limited since early childhood because of a nervous ailment. Two years earlier he had been told that he had coarctation of the aorta, after examination at a large Midwestern medical clinic.

Examination revealed a slightly built, thin young man. The carotid arteries did not pulsate. The heart was not enlarged. No cardiac murmurs were heard. The blood pressure was 160/106. The pulsation of the femoral artery could be felt, but the impulse was of lesser intensity than that of the radial pulse. The blood pressure in the popliteal region was 96/62. The intercostal pulsations were of moderate intensity.

CASE 9.—The patient was an 18-year-old white man with no previous knowledge of cardiac abnormality. He gave a history of active participation in athletics, particularly football, and, to a lesser degree, basketball.

Examination revealed a well-built young man with a ruddy complexion. The carotid arteries could not be seen to pulsate. The cardiac apex was 3 cm. to the left of the midclavicular line in the fifth intercostal space. A loud diastolic murmur was heard at the cardiac apex, the aortic valve, and over Erb's point. The blood pressure was 240/160. The femoral pulsations could not be obtained. The blood pressure in the popliteal area was 140/100. Palpation of the intercostal vessels showed a moderately intense pulsation. The electrocardiogram was normal.
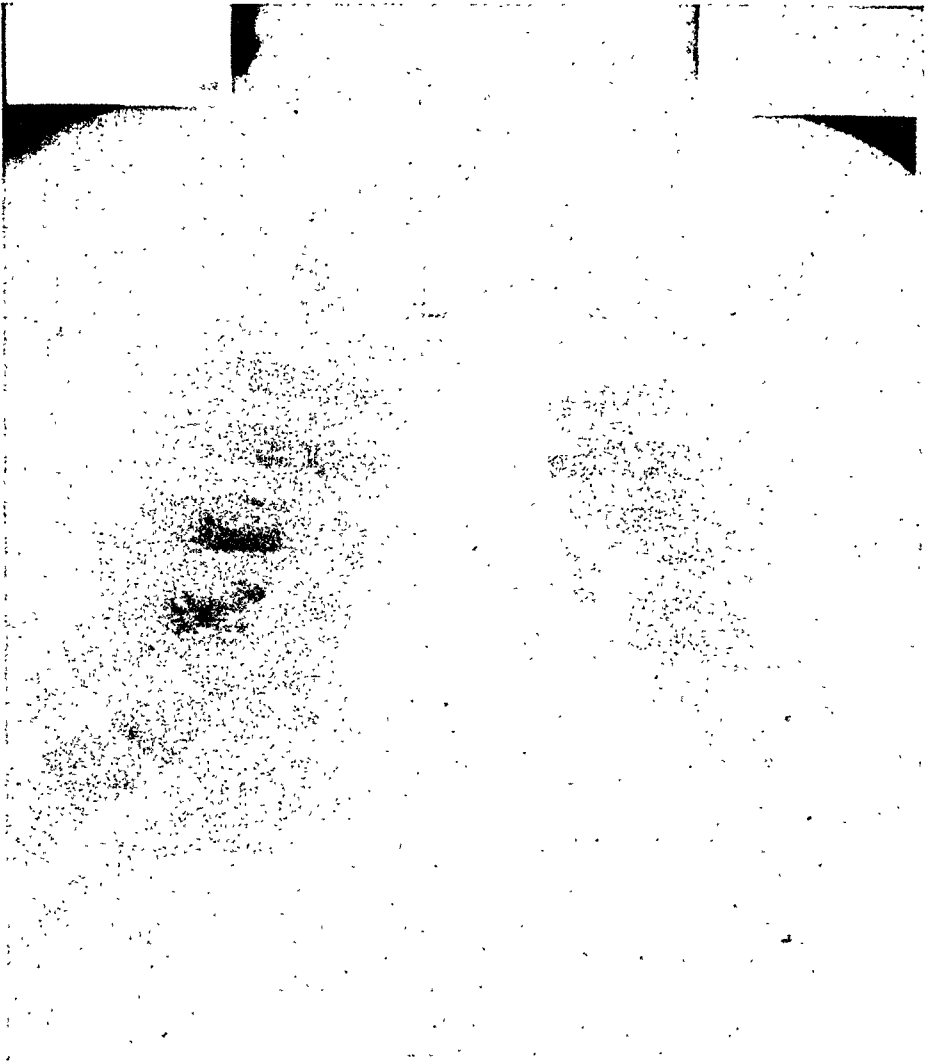
Fig. 8.—Case 8.

CASE 10.—The patient was a 23-year-old white man who had been aware that he had a cardiac lesion since the age of 8 years. Despite this knowledge he had indulged moderately in athletics, including football, boxing, and baseball.

Examination revealed a very well-developed, well-nourished young man. The carotid arteries were pulsating forcibly. The cardiac apex was in the fifth intercostal space in the left anterior axillary line. There was a loud, diastolic murmur at the aortic valve and over Erb's point.

The blood pressure was 184/60. The femoral arteries could not be palpated, and the blood pressure in the popliteal region was not obtainable. The intercostal blood vessels were easily palpable. The electrocardiogram showed a pattern compatible with hypertensive heart disease.
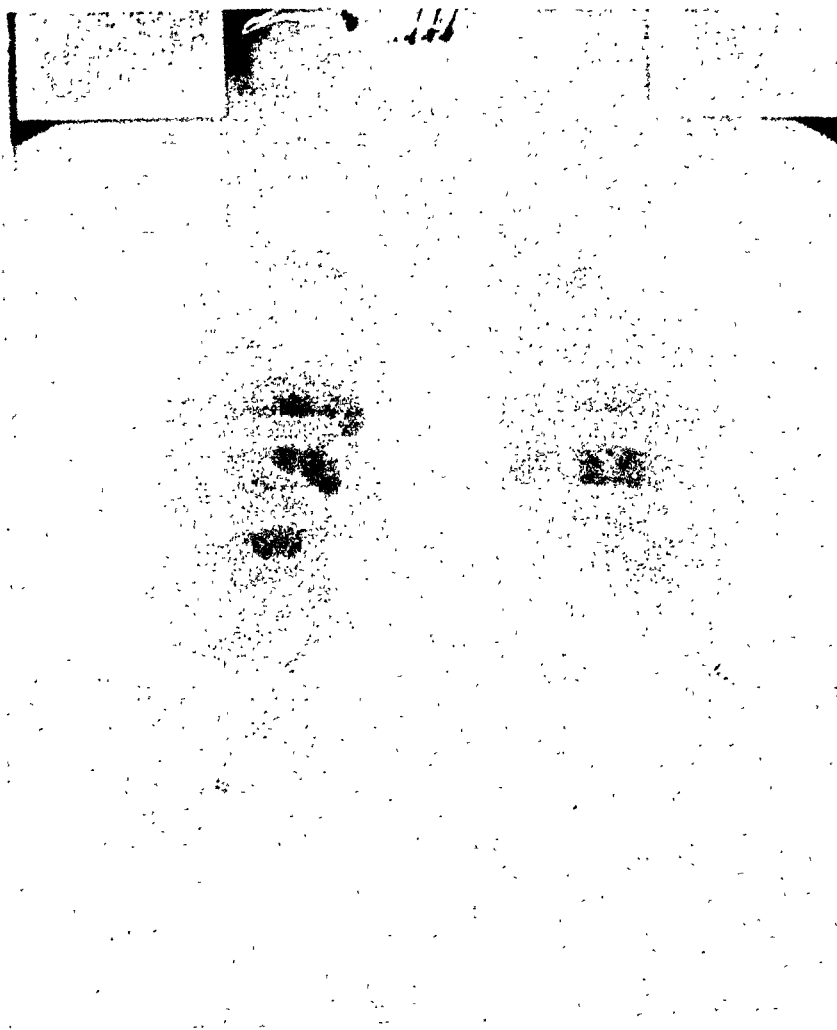
Fig. 9.—Case 10.

CASE 11.—The patient was a 32-year-old white man who had been told that he had hypertension at the age of 22 years. His earlier history showed moderate participation in athletics, and, even after he learned that he had high blood pressure, he had been performing heavy manual labor.

Examination revealed a fairly well-built, young, white man with a very flushed face. The carotid arteries were pulsating strongly. The cardiac impulse was within the midclavicular line in the fifth left intercostal space. Auscultation revealed a soft, blowing, diastolic murmur over the aortic valve which was transmitted to Erb's point. The blood pressure was 214/128. The femoral arteries gave only a moderate impulse to palpation. The blood pressure in the popliteal area was 126/100. The intercostal vessels were easily palpated, and stood out as dilated, wormlike threads over the lateral and posterior aspects of the thorax. The electrocardiogram was normal.

CASE 12.—The patient was a 25-year-old white man who had known that he had some cardiac abnormality since early childhood. Because of this knowledge he had led a very restricted life, and had never indulged in any competitive sports or performed any strenuous physical tasks.

Examination revealed a well-developed, well-nourished, young white man. The carotid arteries were pulsating with moderate intensity. The cardiac apex was within normal limits. Auscultation revealed a harsh systolic murmur at the apex and at the base of the heart. The aortic second sound was markedly accentuated. The blood pressure was 192/70. The pulsations of the femoral artery could not be obtained, and the blood pressure in the popliteal area also could not be obtained. The intercostal vessels could be palpated upon slight pressure on the under surfaces of the ribs. The electrocardiogram showed a pattern compatible with hypertensive heart disease.
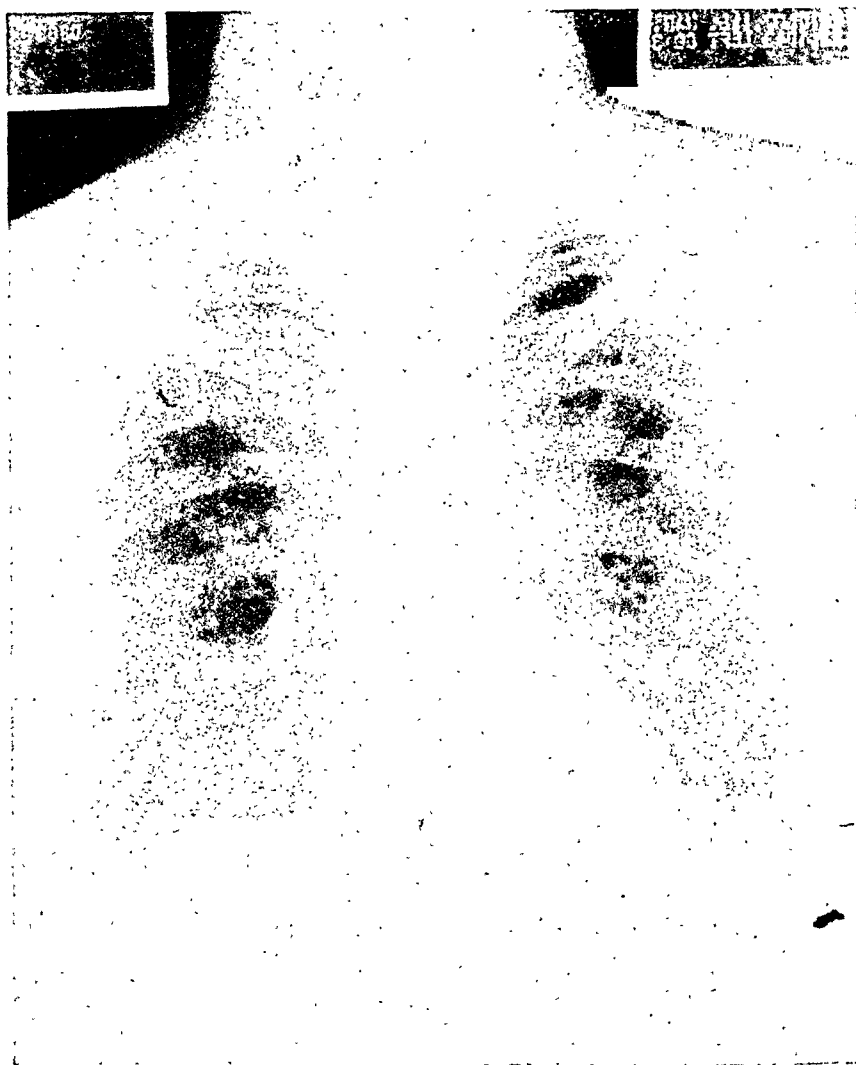
Fig. 10.—Case 11.

CASE 13.—The patient was an 18-year-old white man with no previous knowledge that he had cardiac disease. He gave a history of moderate indulgence in sports, particularly swimming and baseball.

Examination revealed a well-developed, moderately well-nourished, young white man. The carotid arteries were seen to pulsate with moderate intensity. The cardiac apex was in the fifth intercostal space at the
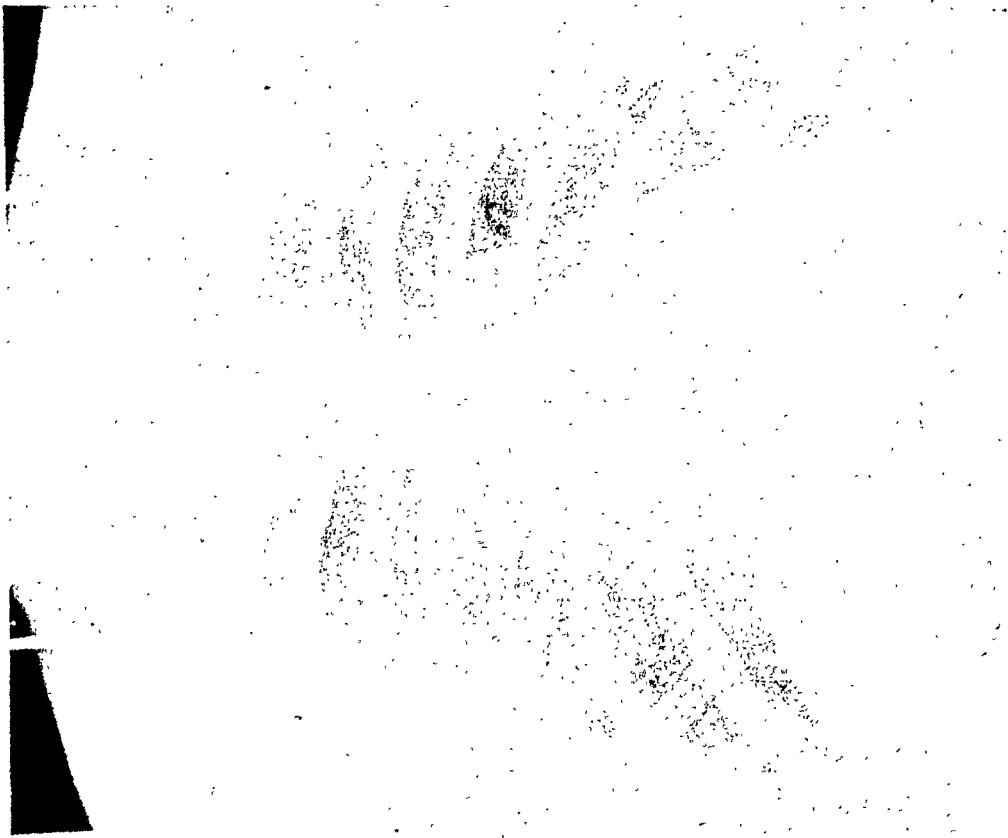
Fig. 12.—Case 13.
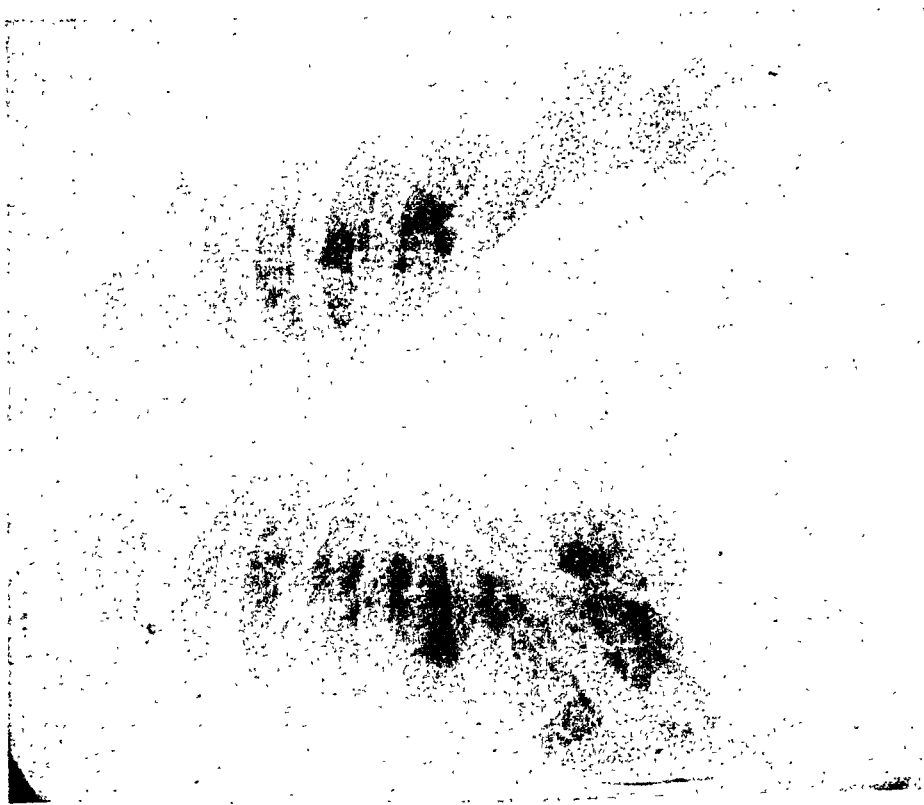
Fig. 11.—Case 12.

left midclavicular line. Auscultation revealed a soft, blowing diastolic murmur at the base of the heart. The blood pressure was 180/90. The femoral artery pulsations were not obtainable, and the blood pressure in the popliteal region could not be measured. The pulsations of the intercostal vessels could be felt with moderate ease. The electrocardiogram was normal.

DISCUSSION

Various methods for the clinical diagnosis of coarctation of the aorta have been advocated. King,[6] in 1926, wrote that pulsation in the interscapular region was the dominant sign of the condition. He stated that the chief value of the roentgenogram was to rule out aneurysm of the aorta. In a later article,[8] he reaffirmed this view by stating that the demonstration of collateral circulation is the most important single clue to the diagnosis of coarctation of the aorta.

In 1932, Dock[9] reported three cases of coarctation of the aorta, and stated that the condition should be looked for in young and middle-aged men with hypertension or hypertension and aortic insufficiency who had pronounced carotid artery pulsations; he advised simultaneous palpation of the femoral and radial pulses, for the femoral pulse is delayed and differs in quality from that in the arms.

In the following year Eppinger and Mittelfart[10] stated that the pathognomonic signs of coarctation of the aorta were a harsh, blowing, systolic murmur over the interscapular region to the left of the spine, heard less intensely over the precordium, and palpable and occasionally visible pulsations over the thorax.

In the same year, Lewis[7] published a series of nine cases of coarctation of the aorta which had been collected over a period of twelve years. In eight of these cases the patients had been seen and the diagnosis had been made clinically, while one was a post-mortem specimen only. He stated, "Of the clinical signs that can be regarded as distinctive there are but two; one is the presence of characteristic anastomotic vessels; the other is the relative weakness and delay of the pulse in the lower limbs. Palpation of the femoral pulse forms and can form no part of a routine examination; it is only undertaken for definite reasons, as when coarctation of the aorta is already suspected, when signs of abdominal aneurysm have been found, or where there are symptoms of inadequate blood flow to the legs. If the diagnosis is to be made it would be wise to examine, as a routine, the femoral pulse in all cases of continued high brachial blood pressure."

Of the thirteen cases here presented, it will be noted that in only three were there pulsations of the femoral artery. In only one of these three cases was the femoral impulse of moderate intensity, and even in this one the impulse did not approach the intensity of the radial artery pulsation. In the remaining two cases the femoral artery pulsation might be classed as slight.

The explanation for the diminution or absence of the femoral pulsation, although blood flow to the lower extremity is present, is well ex-

plained by Bonnet (quoted by Abbott[1]). He states that sensation to the finger does not depend upon blood volume, but on the sharp repercussion of the wave that passes along as the blood is propelled into the aorta. When sudden and abrupt, as normally, the tactile sensation is that of a forcible pulsation. When blood reaches the aorta through a large series of small collaterals, the ascent will be more gradual and the pulse below it correspondingly weaker.

From Table I it might appear that, since intercostal pulsations were present in varying degree in all the cases of coarctation, this would be a better index of the presence of a stenosing aortic lesion. However, intercostal and interscapular vessel pulsations have been noted in cases of uncomplicated aortic insufficiency, and even in extreme tachycardia with or without hypertension. The bounding impulse in the superficial vessels of the thoracic cage in these conditions is not unlike that in many cases of coarctation. Of course, the dilatation and tortuosity of the intercostal vessels do not occur, whereas they are found in well-marked cases of coarctation.

TABLE I

ANALYSIS OF CLINICAL OBSERVATIONS

CASE	AGE (YEARS)	CARDIAC ENLARGEMENT	MURMUR	BLOOD PRESSURE		PULSATIONS	
				BRACHIAL	POPLITEAL	FEMORAL	INTERCOSTAL
1	28	None	Diastolic, base	200/40	0	None	Slight
2	21	None	Diastolic, entire precordium	188/88	0	None	Moderate
3	21	None	None	180/110	110/89	Slight	Moderate
4	19	None	None	210/80	80/40	None	Marked
5	22	None	Diastolic, base	210/90	130/80	None	Moderate
6	21	None	Diastolic, base	170/70	0	None	Slight
7	20	Moderate	Diastolic, base	220/90	0	None	Moderate
8	20	None	None	160/106	96/62	Moderate	Moderate
9	18	Moderate	Diastolic, entire precordium	240/160	140/100	None	Moderate
10	23	Marked	Diastolic, base	184/60	0	None	Moderate
11	32	None	Diastolic, base	214/128	126/100	Slight	Marked
12	25	None	Systolic, entire precordium	192/70	0	None	Moderate
13	18	None	Diastolic, base	180/90	0	None	Moderate

The predominant cardiac murmur was the basal diastolic murmur. This was present in nine of the thirteen cases. Of the remaining cases, no cardiac murmur was heard in three, and a systolic murmur was present in one. The explanation of the presence of the diastolic murmur in such a large number of cases in the present series is difficult. Certainly, it cannot be explained wholly as the result of a bifid aortic cusp, for Abbott's[1] statistics reveal an incidence of only 25.1 per cent of bifid aortic cusps in one hundred eighty-three cases of coarctation of the aorta. Using this as a standard, we should expect, at the most, three patients to have a diastolic aortic murmur. Table I reveals six more than this anticipated number of diastolic aortic murmurs. The possibility of a concomitant rheumatic valvulitis may be considered,

but, in view of the absence of any history of rheumatic fever in these cases, this is unlikely. Perhaps the great pressure within the portion of the aorta proximal to the stenosis, which causes dilatation of the aorta itself, also causes stretching of the aortic ring, with resultant separation of the commissures of the aortic valve and the production of aortic insufficiency.

Although the diagnosis of coarctation of the aorta may be made clinically, the roentgenogram is a very definite diagnostic aid. In some cases the diagnosis may be only hazarded on clinical grounds, and confirmatory evidence from the roentgenogram is essential. The diagnostic value of the roentgenogram in this condition was not realized until the report of Railsback and Dock,[11] in 1929. This was followed, in 1930, by the report of Fray,[12] who also pointed out the value of the roentgenogram in the diagnosis of coarctation of the aorta.

There is a characteristic radiological syndrome consisting of:

1. Absence of the aortic knob.

2. Dilatation of the ascending and transverse portions of the arch of the aorta.

3. Erosion of the lower margin of the posterior portions of the ribs.

4. Roundness or enlargement of the left ventricle.

TABLE II

ANALYSIS OF RADIOLOGICAL OBSERVATIONS

CASE	AORTIC KNOB	AORTIC DILATATION	RIB EROSION	HYPERTROPHY LEFT VENTRICLE
1	Absent	Slight	Moderate	None
2	Absent	Moderate	Slight	None
3	Absent	None	Moderate	None
4	Absent	Moderate	Moderate	None
5	Absent	Slight	Moderate	Slight
6	Absent	Slight	Slight	Slight
7	Absent	None	Slight	Moderate
8	Absent	Moderate	Slight	Moderate
9	Absent	Slight	Slight	Moderate
10	Absent	Moderate	Moderate	Marked
11	Absent	Moderate	Marked	Slight
12	Absent	Slight	Moderate	Slight
13	Absent	None	Moderate	Slight

In the present series the only constant radiological signs were absence of the aortic knob and erosion of the ribs (Table II). The patient with the slightest amount of rib erosion was the one with the lowest blood pressure in the series (Case 8; B.P. 160/106). This coincides with a statement of King,[8] who believed that erosion of the ribs is not necessarily present in typical coarctation of the aorta, and, in the case he cited, the blood pressure was only 123/87. Dilatation of the aorta was found in ten cases of the series. The contour of the left ventricle was normal in four cases, slightly enlarged in five cases, moderately enlarged in three, and markedly enlarged in one. This change in left ventricular contour coincided neither with the degree of elevation of the blood pressure nor with the type of murmur.

Electrocardiograms were obtained in seven of the cases. Five of these were normal, and the remaining two were compatible with hypertensive heart disease. As a diagnostic aid, it would seem that the electrocardiogram is of very little value. The changes observed probably depend directly upon the response of the myocardium to the long-continued strain of blood pressure elevation. This seems likely because the abnormal electrocardiograms occurred in the two cases of longest duration (Cases 11 and 12).

SUMMARY

1. The incidence of coarctation of the aorta is discussed, and the relation of post-mortem and clinical incidence is compared.

2. Thirteen cases of coarctation of the aorta are reported.

3. The clinical manifestations and the constance of these manifestations, as previously reported, are correlated.

4. The roentgenologic and electrocardiographic observations in these cases are analyzed.

CONCLUSIONS

1. Coarctation of the aorta should be suspected in all cases of hypertension, or hypertension and aortic insufficiency.

2. These patients should be examined for absence of femoral artery pulsation or a marked diminution in the strength of the femoral pulsation. Secondarily, an attempt should be made to palpate the intercostal vessels.

3. The significant roentgenologic abnormality is absence of the aortic knob, with confirmatory evidence in the form of rib erosion, aortic dilatation, and left ventricular enlargement.

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ELECTROCARDIOGRAPHIC STUDY OF LATERAL INFARCTION, PROVED AT AUTOPSY

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OMAHA, NEB.

A PREVIOUS paper from the Henry Ford Hospital reported a series of patients with coronary artery occlusion, proved at autopsy, and correlated their electrocardiographic features with the location of the myocardial infarct.[1] These, with additional cases since then, have been reviewed for the purpose of distinguishing the graphic variations associated with lateral, as distinguished from anterior and posterior, infarction.

Other authors have demonstrated the relation of the electrocardiogram to the site of the infarct on the anterior or posterior surface of the left ventricle; Barnes[2] has aptly discussed this subject. The subdivision of the electrocardiogram of myocardial infarction into anterior and posterior types is useful for general diagnostic purposes, and its value would undoubtedly be increased by the addition of a third, or lateral, type to this group.

A number of studies have been made relating to the situation of myocardial infarctions, but, since the incidence of uncomplicated lateral infarcts is small, the electrocardiographic information in proved cases is meager; there are definite reasons for this.

As pointed out by F. J. Smith and his associates, the type of case at autopsy is, in the majority of instances, one of ancient and multiple infarctions, with or without superimposed, recent, single infarction. Judging from our studies, instances of recent single infarction are in the minority. Sprague and Orgain[3] have reported a similar experience in their review of autopsies at the Massachusetts General Hospital. They state that, "Since it is a group such as ours that lives long enough to be studied by the practicing physician it becomes the more important that we discover what such cases show clinically by the electrocardiogram and at autopsy."

The distribution of the coronary arteries to the myocardium is subject to a great number of variations.[4] In general, infarction of the anterior apical surface of the left ventricle is usually produced by occlusion of the anterior descending branch of the left coronary artery; infarction of the posterior basal surface is usually produced by occlusion of the posterior descending branches of the right coronary; and infarction of the lateral midventricular surface is usually produced by occlusion of the circumflex branch of the left coronary artery. Septal

infarcts may occur with occlusion of the septal branches of the left or right coronary arteries, or as part of an anterior or posterior infarct.

Occlusion of the anterior descending branch of the left coronary artery is more common than that of the posterior descending branches of the right coronary artery. Occlusion of the circumflex branch of the left coronary is the least common of these, probably, as suggested by Whitten,[5] because of the position of its first part in the coronary sulcus and above the ventricle. Furthermore, in addition to usually supplying the lateral surface of the left ventricle, branches of this artery may supply the anterior apical or, more frequently, the posterior basal part.[4] Occlusion of the left circumflex is variously reported to occur with an incidence of 5 to 10 per cent. It therefore becomes apparent why uncomplicated lateral infarction is not common.

<center>MATERIAL STUDIED</center>

For the past twenty years the electrocardiograph has been available for use on our patients. During this period approximately 200 persons with cardiac infarction have been examined post mortem. Two conditions reduce the number of cases of completely reliable material for electrocardiographic correlation. First, coronary occlusion may occur without producing myocardial infarction if there is an adequate collateral circulation, or coronary insufficiency, without actual occlusion, may occur and produce infarction if there is transient ischemia. Second, in a large general hospital, several different pathologists will have dictated the protocols with no consistent method of description of coronary or myocardial disease.

In the material studied there were five instances of recent, uncomplicated infarction of the lateral surface of the left ventricle. Infarcts described as extending to either the apical, anterior, basal, or posterior surfaces were excluded. Histologic description of the infarcts confirmed their recent occurrence when this was not established clinically.[6] In all but one there was complete obstruction of the left circumflex artery, and the remaining had no demonstrable occlusion.

A review of the records gave electrocardiographic information on all of these patients, as described in the case reports. The precordial leads were made with the precordial electrode at the cardiac apex, (IV F), and are presented in all instances according to the method recommended by the Committee of the American Heart Association for the Standardization of Precordial Leads.[7] Those illustrated were rephotographed and printed in reverse; the others, as described, required no transposition for this purpose, for they were originally made by the present standard method.

<center>CASE REPORTS</center>

CASE 1.—T. H., a white man, aged 42 years, was admitted to the hospital Feb. 3, 1933, twenty-four hours after the onset of severe substernal pain. He had been having mild chest pain on effort for the previous two weeks. His initial temperature was 98° F., his pulse rate, 80, his respirations, 20, his blood pressure, 150/100, and his leucocyte count, 12,500. The electrocardiogram made the same day was normal except for left axis deviation; no precordial lead was obtained. He had a recurrence of pain forty-eight hours later, and the next day there were a

slight relative elevation of the RS-T segment in Lead I, a depression of the RS-T segment in Lead III, and an inverted T wave in Lead IV. On the seventh day a diphasic T in Lead II and an inverted T in Lead III had developed; the inverted T persisted in Lead IV.

The clinical course was uneventful until, three weeks later, there were another attack of pain, a further fall in blood pressure, and the appearance of a pericardial friction rub. The next day there was inversion of the T wave in Lead I, with a return of upright T waves in Leads II and III and a further inversion of the T in Lead IV. Seven days later an inverted T wave in Lead II had developed. During the ensuing three weeks he had frequent, transient, chest pain and progressive
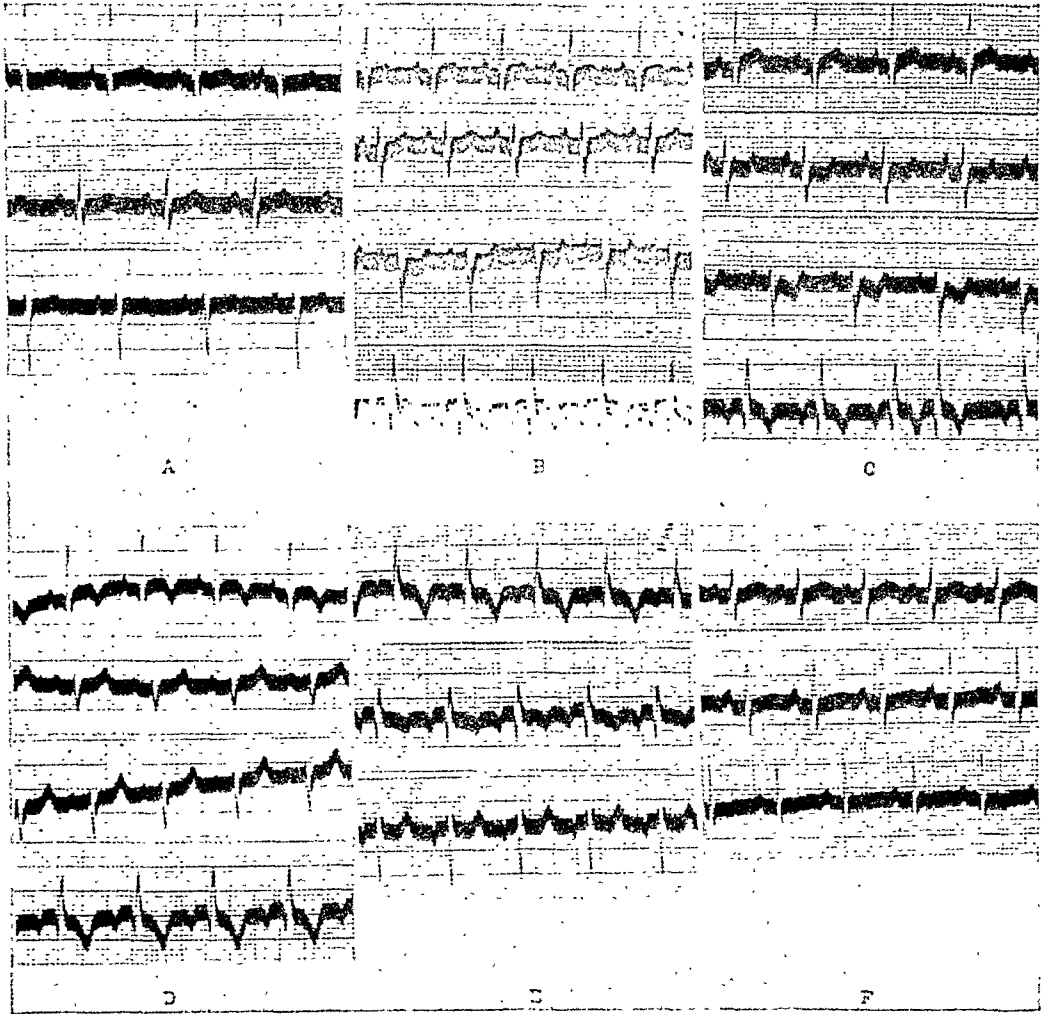
Fig. 1.—Electrocardiograms in Case 1. *A,* Tracing made on first hospital day twenty-four hours after onset of pain. *B,* Fourth day. *C,* Seventh day. *D,* Twenty-eight day. *E,* thirty-fifth day. *F,* Sixty-fifth day.

congestive heart failure. Digitalis was given and brought about slight temporary improvement, but the disease proved fatal on the sixty-sixth hospital day. The standard leads shortly before death were not definitely abnormal. There was no axis deviation or abnormal Q waves, and the T waves in Leads I and II were upright with an isoelectric T in Lead III (Fig. 1).

At autopsy the heart weighed 650 grams. Immediately distal to the origin of the left circumflex an organized thrombus occluded the artery. Further in its course there were more recent thrombi. On the lateral

surface of the left ventricle there was a large, dilated aneurysmal sac, measuring 10 cm. in diameter, whose wall was composed in part by the adherent visceral and parietal pericardium.

CASE 2.—J. H., a white man, aged 55 years, was admitted March 12, 1938, one week after the occurrence of substernal pain of several hours' duration, with a complaint of shortness of breath. The temperature was 100° F., the pulse rate, 120, the respirations, 40, the blood pressure, 110/80, and the leucocyte count, 11,250. Examination revealed mild congestive heart failure. The electrocardiogram showed slight left axis deviation, large Q waves in Leads II and III, an elevated RS-T segment in Leads I, II, and IV, and an inverted T wave in Lead IV. He received no digitalis. Death occurred the next day.

At necropsy the heart was hypertrophied and weighed 900 grams. A recent thrombus completely occluded the left circumflex artery. There was a soft, hemorrhagic area of infarction approximately 10 cm. in diameter on the lateral surface of the left ventricle. The pericardium around this was covered with a fibrinous exudate.

CASE 3.—W. H., a white man, aged 37 years, entered the hospital March 28, 1928, complaining of nausea and vomiting during the previous ten days. There had been no chest pain or symptoms of myocardial insufficiency. The temperature was 98.6° F., the pulse rate, 100, the respirations, 18, and the blood pressure, 250/130. There were a moderately severe secondary anemia and a 4 plus albuminuria, with hyaline casts. The nonprotein nitrogen content of the blood was 240 mg. per 100 c.c. The clinical diagnosis was chronic nephritis with uremia. A routine electrocardiogram showed left axis deviation and an inverted T wave in Lead 1. No precordial lead was obtained. Coma preceded death on the seventh day.

Post mortem, the heart weighed 500 grams. Recent thrombosis of the left circumflex artery, had caused a necrotic infarct "several square centimeters in diameter" on the lateral surface of the left ventricle. The pericardium was covered with a fibrinous exudate.

CASE 4.—C. M., a white woman, aged 53 years, was admitted June 4, 1928, forty-eight hours after the onset of substernal pain. There had been no previous angina of effort. The initial temperature was 98° F., the pulse rate, 100, the respirations, 25, the blood pressure, 125/80, and the leucocyte count, 13,750. Examination revealed mild congestive heart failure. The electrocardiogram showed no axis deviation, a large Q wave in Lead III, and an elevation of the RS-T segment in Lead III, with corresponding depression of the RS-T segment in Lead I. There was no precordial lead. The patient died in an attack of pulmonary edema on the fourth day. She had received no digitalis.

At autopsy the heart weighed 450 grams. A recent, organizing thrombus occluded the left circumflex artery, and a soft, hemorrhagic infarct (unmeasured) occupied the lateral surface of the left ventricle.

CASE 5.—M. E., a white woman, aged 60 years, entered the hospital April 25, 1941, with complaints of shortness of breath and palpitation. There was no history of chest pain. Her symptoms had become more pronounced a few days before admission. She had received digitalis for the previous month. The temperature was 98.6° F., the pulse rate, 80, the respirations, 30, the blood pressure, 160/95, and the leucocyte count, 18,000. The patient had moderate congestive heart failure. The

electrocardiogram substantiated the diagnosis of auricular fibrillation, and showed slight left axis deviation, low voltage of the QRS complexes, and absence of the R wave in Lead IV. Death from progressive heart failure occurred on the seventh day.

At necropsy the heart weighed 550 grams. There was extensive coronary atherosclerosis, but no actual occlusion, with a recent infarct, 5 cm. in diameter, on the lateral surface of the left ventricle.

<div align="center">COMMENT</div>

Electrocardiographically, one can usually recognize patterns of anterior or posterior myocardial infarction, although in numerous instances there are indeterminant features, or these do not indicate the location of the infarct. This may be due to one or more of several factors: the position of the heart in the thorax, the condition of the circulation to the myocardium, the occurrence of previous or multiple infarction, the situation of the infarct in relation to the endocardial or epicardial surfaces, the development of pericarditis with or without effusion, the association of conduction defects, modification by digitalis therapy, and the number of the electrocardiograms and the time at which they were taken in relation to the occurrence of the infarct.

The anterior type is recognized by the development of a prominent Q wave in Lead I, early elevation of the RS-T segment in Lead I, with reciprocal depression of this segment in Lead III, later inversion of the T wave in Lead I, and elevation of the RS-T segment, with later inversion of the T wave, in Lead IVF. In the posterior type there are a prominent Q in Lead III and frequently in Lead II, early elevation of the RS-T segment in Lead III, with reciprocal depression in Lead I, and later inversion of the T in Lead III, or Leads II and III. With posterior infarction the precordial lead is less likely to change, but, if it does, there is usually depression of the RS-T segment, with the T wave remaining upright.

When infarction involves both the anterior and posterior surfaces of the left ventricle, the effect of the anterior one predominates in the electrocardiogram, as reported by Wolferth, Wood, and Bellet.[8]

Recently these authors[9] have reported a series of cases wherein they defined a lateral type, characterized by depression of the RS-T segment in Leads I and II (commonly, although not universally present), absence of signs of infarction in Lead III, and depression of the RS-T segment in the precordial lead. Their conclusion, based on one case of uncomplicated lateral infarction, proved at autopsy, with a second probable case, was that lateral infarction does occur anatomically, and that, since characteristic anterior and posterior types exist, it is reasonable to suppose that there is a lateral type, also.

Not one of our autopsy cases presented these features, nor was there a single consistent pattern. In Case 1, with serial electrocardiograms, there were the features of both anterior and posterior types, with a predominant anterior pattern. It is interesting to note that the standard

leads on the day before death were not definitely abnormal. Case 2 resembled Case 1 in that there was a mixed anterior and posterior pattern. Case 3 was of a definite anterior, and Case 4 of a definite posterior, type. In Case 5, in which there had been previous digitalis medication, there was no clinical evidence of recent infarction. This patient also had auricular fibrillation, an arrhythmia that Wood and his associates say occurred with unusual frequency in their cases.

The literature contains information on the correlation of autopsy observations with electrocardiograms. There is usually no special reference to the type of pattern associated with lateral infarction. A summary of a group of these investigations, wherein such infarcts are described, is presented in Table I. In most instances the corresponding electrocardiograms are noted as conforming to one type or another without further elaboration. When these are stated to be atypical and are more completely described, there is no conformation to a "lateral type." However, as reported by Wood, et al., the electrocardiographic features of the acute lesion may subside very rapidly and become unrecognizable.

TABLE I

SUMMARY OF REPORTS BY VARIOUS AUTHORS LISTED AMONG THE REFERENCES*

AUTHOR (REFERENCE) NUMBER	TOTAL NUMBER OF CASES	TOTAL NUMBER OF LATERAL INFARCTS	AGE OF INFARCTS: OLD NEW		ELECTROCARDIOGRAM TYPE ANTERIOR POSTERIOR ATYPICAL NORMAL			
10.	168	3	?	?	1	2		
11.	149	2	1	1	2			
3.	131	2	1	1 combined	1		2	
12.	34	1		1				1

*This summary represents the number of autopsy cases, the number of lateral infarcts with electrocardiographic study, and the electrocardiographic pattern. The atypical patterns were associated with defects in conduction: in one, auricular fibrillation, in the other, intraventricular block.

SUMMARY

1. There is a small incidence of fresh, uncomplicated infarction of the lateral surface of the left ventricle, as ascertained by a study of autopsy cases.

2. There was no characteristic electrocardiographic pattern associated with lateral infarction analogous to anterior and posterior types in our series of cases.

The autopsy records were reviewed with Richmond W. Smith, M.D., Detroit, Michigan.

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ADDENDUM

Since this article was submitted, a discussion of the subject by Thomson and Feil has been published.[13] They presented a larger number of cases of lateral infarction, and their conclusions were in favor of a typical electrocardiographic pattern as proposed by Wood, Wolferth, and Bellet. In their group with "typical" electrocardiograms, as presented, Case 1 had a depressed S-T segment in Leads I, II, and IVR, and Case 2, a depressed S-T segment in Lead IVR. The remaining two cases in this group could have been included in their group of lateral infarctions with "atypical" electrocardiograms, for both had abnormalities consistent with a mixed anterior and posterior pattern.

THE EFFECT OF DRUGS ON THE SURFACE CAPILLARIES OF THE MACACA RHESUS

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INTRODUCTION

THE recording of over-all vascular responses gives little information concerning the changes occurring within a specific portion of the peripheral circulation. An attempt is made here to indicate the direct or reflected responses of the capillaries, as such, to certain drugs. Direct observation of the capillaries in various sites on the human skin has been widely used. Evaluation of the observations is difficult because of the lack of standardization in recording them, and in the maintenance of a fixed experimental environment. Since capillary microscopy permits direct observation of the changes in the most distal portion of the vascular tree, it holds obvious advantages as an approach to the study of the responses of the capillaries to drugs.

When a capillary is viewed by direct microscopy in vivo, with the magnification of 60 and 100 times which we employed, the endothelial tube limiting the capillary cannot be distinguished. The capillary is seen because of the blood contained within it. Variations in the diameter of the column of blood due to drugs or other causes are actually the alterations which are interpreted as changes in the diameter of the capillary.

It becomes possible, therefore, in observing a given field, to ascertain the morphology of the capillaries present and the nature of the blood flow within them. Differentiation between arterial and venous limbs of the capillaries is made possible by the difference in diameter and the direction of blood flow. A small segment between the arterial and venous limbs, of greater diameter than either, may frequently be distinguished, and is called the "transitional limb."

METHOD

Four female macaques, varying in weight between 4.5 and 5.5 kg., were used. The observations were made on the capillaries of the skin at the base of the fingernail in the right forelimb.

The widespread physiologic influences which affect the peripheral capillaries can be interpreted at present only to a limited degree. Control was attempted for the following factors:

1. Diet was held constant for four weeks prior to the first observations, and was maintained fixed.

2. Fluid intake was fairly constant, in that the monkeys were offered 400 c.c. of water per day, of which 300 to 400 c.c. were consumed.

3. The room temperature was maintained between 25° and 30° C. during observations.

4. Observations without anesthesia were attempted by the use of wide arm sleeves to fix the limbs firmly and not impair the circulation. Because of changes due to struggling, and possible psychogenic changes, it was found necessary to employ a general anesthetic. This was given as nembutal intraperitoneally in doses which varied between 0.55 and 1.2 c.c. per kilogram of body weight; the smallest dose which would produce anesthesia was used in each case.

The state of the sexual cycle was not given special consideration, for the observations were concerned essentially with relative changes during the given experiment.

In order that the hand would be held in a fixed position most favorable for access to the fingernail bed, a dental compound glove was molded to the hand of each monkey and employed during observation. These gloves covered the hand from above the wrist to the base of the terminal phalanges, but did not impair the circulation. The hairs of the fingers which overlapped the field of observation were cut with scissors. The area was cleansed by wiping with cedar oil.

The anesthetized animal in each instance was placed in the semi-prone position with the right arm extended at approximately heart level and the hand encased within the compound glove. Observations were carried out with a Leitz capillary microscope at magnifications of 60 and 100 times. Photographs were taken in some instances, using a Leica camera equipped with a beam-splitting mechanism. The light source was a 6-volt, 5-ampere lamp encased in an air-cooling system, and the light was passed through a green and a yellow Corning heat-absorbing glass filter. This setup, as checked by direct thermometry, gave only slight changes in temperature at the site of observation. With a thermometer placed horizontally, and the mercury base at the point of greatest light concentration and coinciding with the position of the monkey's finger during observations, there were changes of 1.4° and 1.1° C. in five minutes and six minutes, respectively.

Since the method is subjective, and open to the errors inherent in such an approach, all experiments were repeated at least twice and observations were made independently by the writers.

The different drugs were administered only by direct intravenous injection into the superficial leg veins; 1 c.c. was the largest quantity of fluid given at a single injection.

<div align="center">OBSERVATIONS</div>

Four series of observations on the effects of nembutal anesthesia were made; the monkey was fully anesthetized in three, and remained partially responsive in the fourth. The capillary loops showed slight blurring and minor diameter changes, such as slight narrowing of the arterial limbs and slight widening of the venous limbs.

Sterile saline in 1 c.c. doses, of pH 5.9, was injected intravenously in two instances. No changes in diameter or stream were noted.

1. Drugs considered to act on the parasympathetic nervous system.

A. *Pilocarpine.*—Four series of observations with intravenous

doses of 0.5 mg. of pilocarpine showed a consistent narrowing of the venous limbs, and either a slight slowing or no change in the blood flow. Narrowing of the arterial limbs was noted in one of these observations.

B. *Acetyl-β-Methylcholine.*—Eight series of observations with intravenous doses of acetyl-β-methylcholine, varying from 0.25 to 2 mg., showed consistent changes in the indistinctness of the capillary outline, widening of the arterial and venous limbs, and marked slowing of the stream. "Fading" of the capillary outline occurred within one-half minute after doses of 1 mg. and over, and was followed by return of capillary visibility and the previously mentioned changes.

C. *Atropine.*—Twelve series of observations with intravenous doses of atropine sulfate are reported, two of which followed pilocarpine injection. When given alone in eight instances, in doses varying between 0.5 and 5 mg., there were a consistent, slight widening of the transitional limb, and occasional widening of the venous and arterial limbs. In two instances, with doses of 0.25 mg., the only change was a slight narrowing of the arterial limbs. Marked widening of the entire capillary loop followed the administration of atropine thirty-five minutes after pilocarpine had been given, and, in another instance, thirty-nine minutes after pilocarpine, atropine produced marked widening of the venous and transitional limbs with but slight widening of the arterial limb.

2. Drugs considered to act on the sympathetic nervous system.

A. *Epinephrine.*—Sixteen series of observations were made after the intravenous injection of epinephrine hydrochloride in doses varying from 0.0002 to 0.5 mg.

a. A dose of epinephrine of 0.001 mg., or over, induced complete blanching and disappearance of the capillaries in the field. With return of the capillary to view, markedly narrowed venous and transition limbs were first noted, followed soon after by reappearance of similarly narrowed arterial limbs.

b. A dose of epinephrine of 0.00075 to 0.0003 mg. induced narrowing of the arterial limbs, followed by narrowing of the venous and transition limbs. The stream of blood was slowed.

c. A dose of 0.0002 mg. of epinephrine produced no change in the capillary loops.

B. *Ergot group.*—Five series of observations are reported with ergotamine, ergonovine, and ergotoxine.

a. In two instances, after the injection of 0.25 and 0.50 mg. of ergotamine, the capillaries showed narrowing of the arterial limbs, fluctuations in distinctness of outline, and slowing of the stream.

b. In two instances, after injections of 0.20 mg. of ergonovine, there were narrowing of the arterial limbs and fluctuating distinctness of the capillary outline.

c. In one instance, after the injection of 0.50 mg. of ergotoxine, there were narrowing of varying degree of the arterial limbs and fluctuating distinctness of the capillary outline.

3. Miscellaneous.

A. *Nicotinic acid.*—Doses of 5 mg. and 10 mg. of nicotinic acid were administered intravenously. The smaller dose was found to give a slight widening of the entire capillary loop, and the large dose induced a more marked widening of the arterial limb.

B. *Nicotamic acid.*—A dose of 5 mg. of nicotamic acid, in injected intravenously, induced an increased speed of blood flow and widening of the entire capillary loop.

TABLE I

SUMMARY OF EFFECTS OF SPECIFIC DRUGS ON THE SURFACE CAPILLARIES
OF THE MACACA RHESUS

DRUG	ART. L.	TRANS. L.	VEN. L.	BL. FLOW
Pilocarpine	Nar.		Nar.	Dec.
Acetyl-β-Methylcholine	Wid.		Wid.	Dec.
Atropine	Wid.	Wid.	Wid.	
Epinephrine	Nar.	Nar.	Nar.	Dec.
Ergot	Nar.			Dec.
Nicotinic acid	Wid.	Wid.	Wid.	Inc.

Art. L. = Arterial limb of the capillary.
Trans. L. = Transitional limb of the capillary.
Ven. L. = Venous limb of the capillary.
Bl. Flow = Blood flow through the capillary.
Nar. = Narrowed capillary limb.
Wid. = Widened capillary limb.
Dec. = Decreased blood flow.
Inc. = Increased blood flow.

DISCUSSION

Capillary blood vessels are described histologically as tubes about 8 micra in diameter, formed by a single layer of endothelial cells, and in which muscle elements are lacking. Intercellular cementing substance is interposed along the margins of the endothelial cells.[1] Rouget cells,[2,3] which are believed to represent specialized contractile elements, are distributed at intervals along the capillaries. The blood flow is from the arterial to the venous limb of the capillary loop. Arteriovenous anastomoses, with muscular walls and rich autonomic innervation, are abundant in the fingers and palm of the hand, and act as special sluice gates to by-pass the capillary bed.

For direct capillary microscopy in man, the capillaries of the skin and accessible mucous membranes are utilized. In the region of the fingernail bed (at the base of the cuticle) and the inner surface of

the lip, observation of longer capillary limbs is possible because they tend to lie horizontal to the external surface.

In three of the four monkeys studied, the capillary forms at the fingernail bed showed meandering of the limbs, shorter arterial limbs, and venous limbs, and close proximity to the subpapillary plexus. These capillaries resembled the inhibited developmental form, or "archicapillary," described in man by Jaensch,[4] and are similar to those in cases of mongolism[5] and pituitary disturbances of the Fröhlich type.[6-8] The fourth monkey had capillary loops of hairpin shape, closely similar to the so-called human capillaries in the same region.

Reference to the table in the preceding section, summarizing the effects of the drugs on the capillaries, indicates their possible division into two main groups. Epinephrine, pilocarpine, and ergot produced narrowing of the capillaries, whereas atropine, nicotinic acid, and acetyl-β-methylcholine caused widening of the capillaries.

1. Drugs causing narrowing of the capillaries.

Epinephrine in doses sufficient to induce a pressor response acts by direct myocardial stimulation, increased heart rate, and by constriction of the arterioles.[9, 10] The range of doses employed in this study, i.e., 0.0003 mg. to 0.5 mg., induced a narrowing of the entire capillary. Reduction of the injected dose in two instances to 0.0002 mg. gave no observable change in the capillaries. With minute doses intravenously in animals or subcutaneously in man, a fall in diastolic pressure caused by vasodilatation has been observed.[11] In the ear of the rabbit, blanching of the capillary fields after the administration of epinephrine was observed by Meltzer and Auer.[12] Subsequent hyperemia of the central vessel and arterioles occurred in some instances, but no mention is made of similar capillary changes. Studies of the capillaries in man after the administration of 1 mg. doses subcutaneously showed narrowing with no subsequent dilatation, although the observation was carried on for over one hour.[12, 14] There is no direct evidence in the literature that capillary widening is caused by epinephrine; the evidence that vasodilatation may occur is based essentially on plethysmographic studies indicating over-all vascular changes in the part,[15-17] and on thermocouple studies indicating temperature changes in the muscle.[18]

The action of pilocarpine on the peripheral circulation has not been extensively investigated. It is difficult to explain the observation reported here of decreased diameter of the capillary limbs and no change or slight decrease in blood flow, rather than the expected peripheral vasodilatation. Although the autonomic responses to pilocarpine are considered to be due to its direct action on cells innervated by postganglionic cholinergic fibers, some apparently anomalous reactions of the cardiovascular system have been reported.[19, 20] It has been suggested by Heaton and MacKeith[21] that the anomalous effects on the circulation may possibly be explained by stimulation of the preganglionic sympathetic fibers by pilocarpine.

Diameter and blood flow changes in the peripheral capillaries at the fingernail bed in man have been reported after the administration of ergotamine tartrate to patients with migraine.[22] The mechanism of the action of ergotamine tartrate is believed to be a stimulation of the myoneural junctions of the motor sympathetic nerves.[23] This action is consistent with the observed capillary narrowing.

2. Drugs causing widening of the capillaries.

Doses of atropine between 0.5 and 5 mg. were found to induce small increases in capillary diameter. With doses of atropine less than 1 mg. there was, in some instances, a decrease in the diameter of the arterial side of the capillary. The action of the drug may be peripheral, as a direct vascular effect. Raymond-Hamet,[24] in studies on dogs, concludes that atropine may act directly on the smooth muscle of vessels or their terminal innervation. Another theory holds that dilatation of cutaneous blood vessels after atropine (atropine flush) is a compensatory mechanism to permit heat loss, and thus offset the rise in temperature which atropine induces because of the suppression of sweat. It has further been considered that atropine flush follows dilatation of arterioles from stimulation of the vasodilator center. Lewis,[25] however, has shown that a "flush," in general, is related to changes in the subpapillary plexus, and not to increased blood flow or diameter of the capillaries. Marrazzi[26] believes that atropine acts at the sympathetic ganglia to block tonic vasoconstrictor effects. The observations reported here with direct microscopy may be correlated satisfactorily with this conclusion. No explanation can be offered for the fact that there was a more marked increase in capillary diameter when atropine was administered subsequent to pilocarpine.

The increased peripheral capillary diameter and increased blood flow after nicotinic acid administration are consistent with the reported clinical observations. Spies and his co-workers[27, 28] have noted the occurrence in man of increased temperature, flushing, burning, and itching after oral or intravenous doses of nicotinic acid, affecting especially the skin of the face and upper part of the trunk. Similar changes have been reported by Atkinson.[29] The mechanism of this nicotinic acid side action is not known, although the reaction is seemingly roughly proportional to the dose.[30]

The observations on acetyl-β-methylcholine reported here, namely, an increase in the arterial and venous capillary limb diameters, are consistent with those recorded in the literature. Doses of 20 mg. in man, administered subcutaneously or intramuscularly, or larger doses by mouth, give a transient fall in blood pressure and the sensation of warmth and flushing.[31] A rise in digital skin temperature has been noted by Goldsmith[32] after oral doses of acetyl-β-methylcholine; a similar rise in skin temperature has been noted after iontophoresis.[33] The portion of the circulatory tree involved in these responses is not specified. An explanation that may be offered for the absence of in-

crease in blood flow through the observed peripheral skin capillaries is the possibility of increased flow through the unobserved arteriolovenous anastomoses.

Diameter changes in capillaries after drug administration may be the result of direct effects on the limbs of the capillaries, or reflections of changes occurring in the arterioles or veins. Widening of the arteriole, when associated with increase in blood flow, may induce passive widening of the arterial capillary limb. Diameter changes of the limbs of a capillary, however, may be due to the resultant balance of vasoconstrictor and vasodilator impulses, or thinning or swelling of the endothelial cells.[34, 35] The method employed here does not yield any definite clue as to which of the mentioned mechanisms may be involved in the change in capillary diameter. These drugs which are known to act on the autonomic nervous system may be considered to transmit their capillary effect over the autonomic pathways.

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ELECTROCARDIOGRAPHIC CHANGES OF IMPENDING INFARCTION, AND THE ISCHEMIA-INJURY PATTERN PRODUCED IN THE DOG BY TOTAL AND SUBTOTAL OCCLUSION OF A CORONARY ARTERY

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INTRODUCTORY REMARKS

IN A previous communication[1] we have described the manner in which the electrocardiographic pattern of ischemia and injury may be recorded. When a segment of the anterior descending branch of the dog's left coronary artery is dissected through a small hole in the pericardial sac and a ligature is passed around the artery, the vessel may be occluded totally or subtotally, as desired, by applying tension on the ligature. An essentially unipolar lead is employed, with the exploring electrode placed upon the anterior (or anterolateral) surface of the pericardial sac superjacent to the terminals of the dissected artery, and the indifferent electrode on the left foreleg. The choice of galvanometer terminals is always such that a relatively positive sense of the potential at the exploring electrode, as compared with that at the indifferent electrode, produces an upward movement on the completed record. Continuous recordings are made before, during, and after brief experiments, or at frequent intervals during and after occlusions which last longer than ninety seconds. The resulting electrocardiographic changes are conveniently referred to as the ischemia-injury pattern.[1,2] It is our present purpose to report the effect on the ischemia-injury pattern produced by subtotal occlusion, and to discuss some of the implications suggested by the modifications of the pattern as they appear to concern certain electrocardiographic problems encountered clinically.

METHOD AND MATERIAL

The method of preparation of the animal was similar to that described in a previous communication.[1] Some refinements are noteworthy, however. A good exposure of the pericardial sac is obtained by dividing one or two costochondral cartilages before the incision is spread open. The cotton foot of the exploring electrode is a thin, circular disc, 1 cm. in diameter, attached to a cotton wick. Only the disc is permitted to touch the animal at the desired region of the pericardial surface. Momentary contacts with the chest wall or with the lung will produce disturbing artifacts on the completed record. In the experiments reported. an accessory lead was recorded simultaneously. The

method of taking the accessory lead varied with the particular preparation. At times it was of the semiunipolar variety, with the exploring electrode in the subcutaneous tissues superjacent to the right ventricle. At other times it was of the essentially unipolar variety, with the exploring electrode placed directly on the pericardial sac over the posterolateral aspect of the left ventricle. In one animal Lead II was recorded simultaneously, and, in another animal, Lead I was used. Twelve young, medium-sized dogs were used, and were sacrificed at the end of four to six hours.

RESULTS

Dogs 10 and 11 died during the course of preparation. Dog 6 developed auricular tachycardia with a rate of 180 per minute. During the course of experimentation with total occlusion,[1,2] we have had three animals whose hearts acted in a similar way. All yielded atypical occlusion patterns which closely resembled one another. Although we are not prepared to discuss these patterns at the present time, it appears that a high rate of beating is associated with an alteration in the dynamics of coronnary flow which is reflected in ischemia-injury pattern of occlusion. Dog 8 yielded curves of the kind we have interpreted as evidence that the exploring electrode had been placed superjacent to a region of the myocardium not involved during occlusion by the expanding zones of ischemia and injury. This might have been anticipated from previous experience, for in this animal the anterior descending branch was observed to divide early into two subdivisions of approximately equal size. Usually, the inferior subdivision is considerably smaller. Dissection of both subdivisions with simultaneous occlusion of each subsequently yielded satisfactory patterns. The remaining seven animals likewise yielded results of a uniformly predictable character.

Diversion of T in Stages.—The curves displayed in Fig. 1 show a negative T, obtained after arterial dissection, which undergoes gradual reversion after an intravenous injection of 0.12 Gm. of theophylline with ethylenediamine.[2] Shortly after the reversion, subtotal occlusion was carried out in eight stages by intermittently increasing the tension on an elastic band, looped about the dissected artery. A strip was recorded commencing about thirty seconds after each increase in tension. The result is shown in Fig. 2, in which inversion of T is observed to occur in eight stages. The inverted T in Stage 8 is comparable in form to that observed before theophylline reversion (Fig. 1). The interval over which the inversion stages extend is approximately ten minutes. It is recalled that the homologous inversion which follows sudden, complete occlusion[2] is obtained in about thirty seconds. In the last four stages shown in Fig. 2 there is an undulating variation in the amplitude of T which is synchronous with the artificial respiratory movement of the lungs and mediastinum. The smaller T deflections are associated with the taller QRS deflections, and, conversely, the taller T deflections are associated with the smaller QRS deflections. Undulating variations
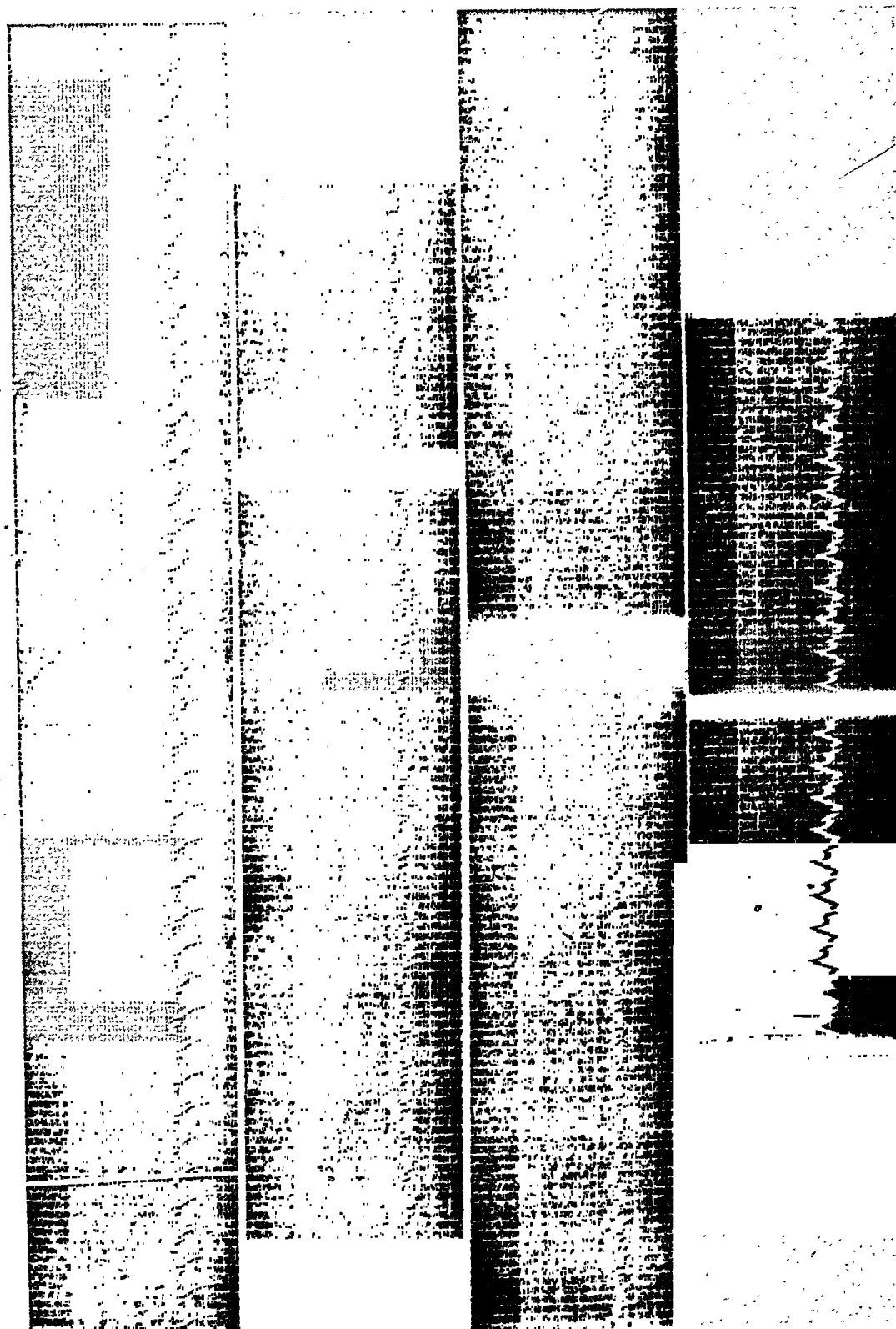
Fig. 1.—An intermittent recording of the reversion of T from a negative to a positive form after the intravenous injection of 0.12 Gm. of theophylline with ethylenediamine. The exploring electrode was in contact directly with the heart's surface 1 cm. above the apex on the anterior wall of the left ventricle. The injection was completed at the time signal in the top strip. The QRS deflections are rapid and hard to make out. R reaches to the top of the strip and S moves off the bottom of the strip. A small Q grows to 4 mm. in amplitude by the end of the recording. The time lines are 0.1 second apart, and the standardization is ¹⁄₆ normal.
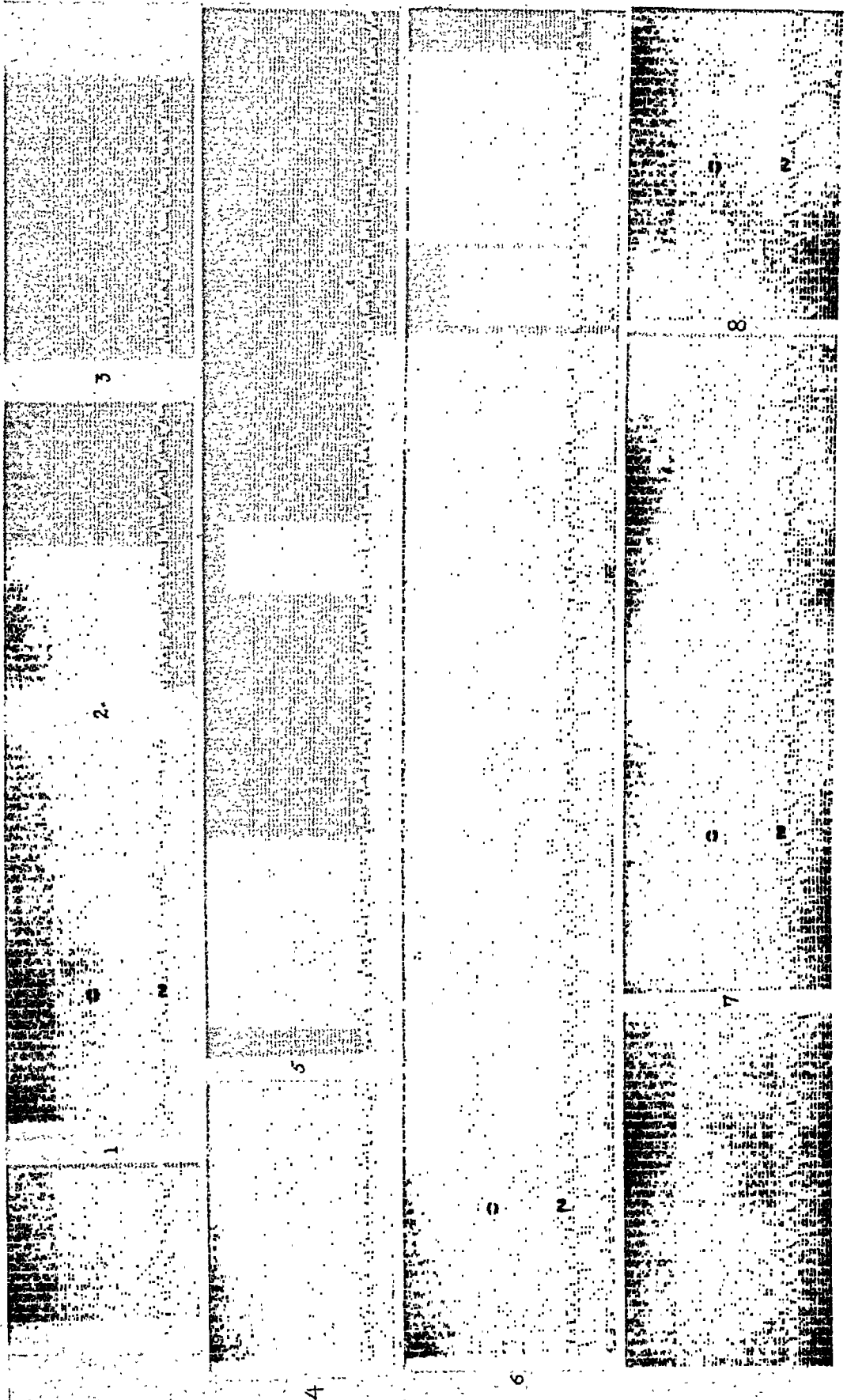
Fig. 2.—A continuation of the experiment started in Fig. 1. Read from above down, and from left to right: First strip is a control before starting subtotal occlusion in eight stages. Before each of the remaining eight strips the elastic ligature was tightened. Note the inversion of T in stages. Note the undulating change in the form of T (synchronous with the respiratory movement). QRS remains practically unchanged throughout. Time and standardization are the same as in Fig. 1.

in the amplitude of QRS which are synchronous with the respiratory movement are observed to occur continuously throughout all of our experiments. They are extracardiac in origin, and are associated with the respiratory variation of the conductivity of the medium surrounding the heart. If the T-wave changes depicted in Fig. 2 are to be ascribed to the same cause, they should be like in kind, and should vary directly with the QRS changes. Actually, the T-wave changes, although they are synchronous with the respiratory movement, are unlike in kind, vary inversely with the QRS changes, and occur only during the subtotal occlusion period. We ascribe the undulating form
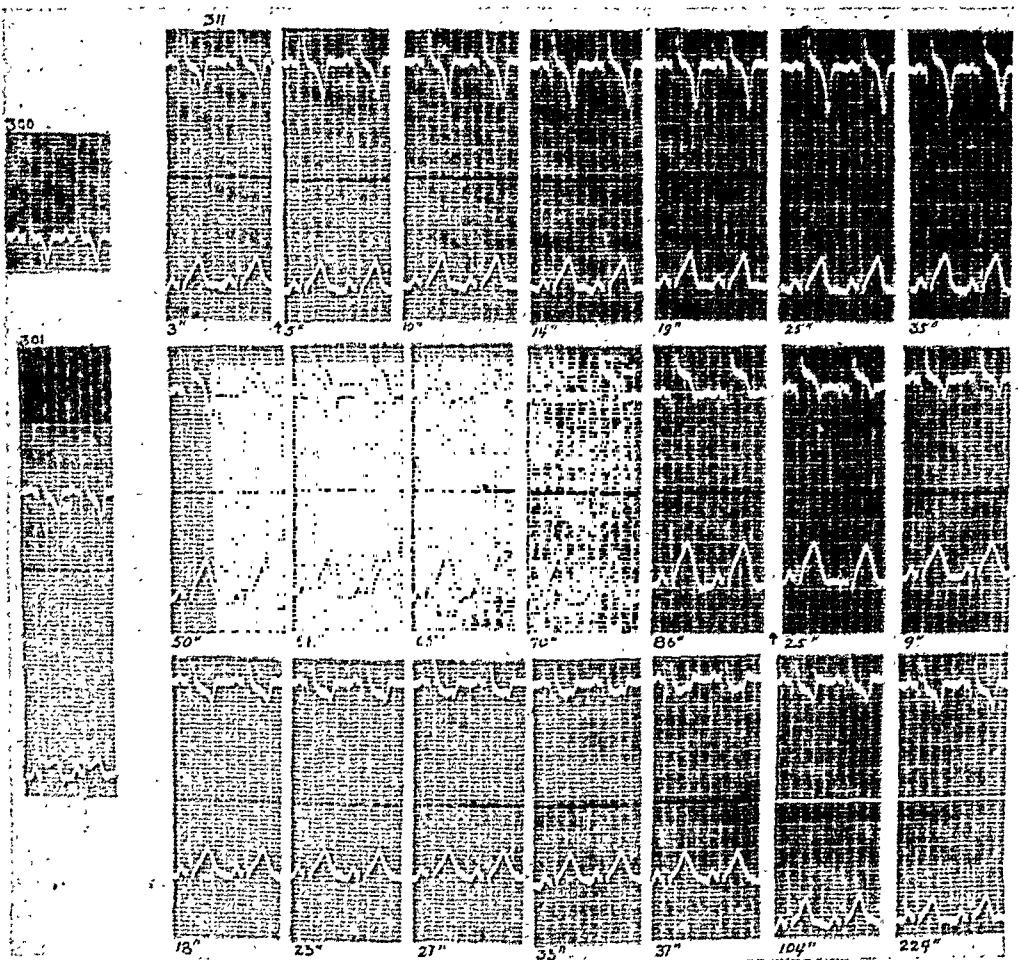
Fig. 3.—Complete occlusion for ninety seconds. Strip *300* is a control recorded before opening the chest. The exploring electrode is in the subcutaneous tissues superjacent to the apex of the left ventricle. Strip *301* is a control taken before arterial dissection. The exploring electrode of the main (top) lead was on the anterolateral aspect of the pericardial sac superjacent to that part of the free wall of the left ventricle irrigated by the artery which is as yet undissected. The exploring electrode of the accessory (bottom) lead was in the subcutaneous tissue superjacent to the free wall of the right ventricle. Reading from left to right and from above down are strips cut from a continuous recording made before, during, and after occlusion of the anterior . . . . . of the left coronary artery. The first strip is the postdissection cc . . . . . . rrows indicate the times at which occlusion started and ended, respectively. The figure under each strip indicates the time in seconds before occlusion started, after occlusion started, and after occlusion ended, respectively. The pattern of the main lead is a typical negative T pattern. Note that only minor changes appear in the accessory lead. The time lines are 0.1 second apart, and the standardization is ½ normal for the main lead, and normal for the accessory lead. In the main lead the top of the R deflections was sacrificed to conserve space. See text.

of T to the varying degree of subtotal occlusion produced by the rise and fall of the heart with respiration and with respect to the fixed extremity of the elastic ligature.* After release of the subtotal occlusion the inverted T gradually became positive.
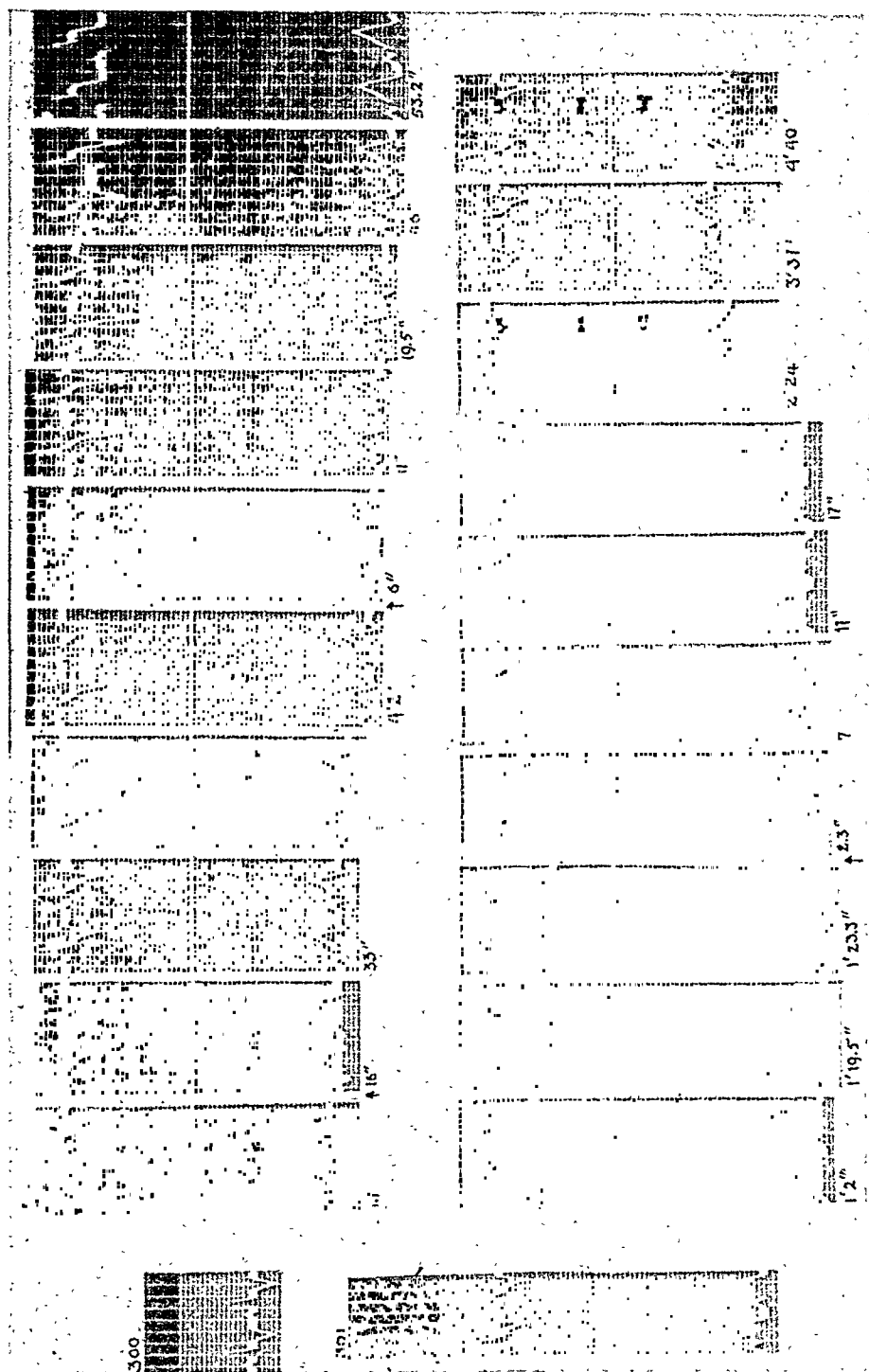
Fig. 4.—A continuation of the experiment commenced in Fig. 3. The two solid rows of strips are, reading from left to right and from above down, from a continuous recording made before, during, and after subtotal occlusion of five minutes' duration and total occlusion for ninety seconds. The three arrows indicate, respectively, the times at which subtotal occlusion started, at which total occlusion started, and at which occlusion ended. The figures under each strip indicate, respectively, the time before subtotal occlusion started, the time after subtotal occlusion started, the time after total occlusion started, and the time after occlusion ended. The dash denotes minutes, and the double dash, seconds. Time and standardization same as for Fig. 3.

Prolonged Diversion of T.—Fig. 3 displays strips which were cut from a continuous recording made before, during, and after ninety seconds of complete occlusion. The exploring electrode of the accessory lead

*This is the only experiment in which an elastic ligature was used, and in which the exploring electrode was placed directly upon the heart's surface.

(lower curve) was superjacent to the anterolateral wall of the right ventricle. The tall R deflections of the upper curve are removed to conserve space. The first arrow indicates the time at which sudden, total occlusion was commenced; the second arrow indicates the time at which the occlusion was released. The ischemia effect was maximum twenty-five seconds after the occlusion commenced. The general form of the pattern is typical of the negative T variety.[1] The animal (Dog 3) was the only one of the series of twelve to display a negative T deflection in the control of the main curve recorded *before* arterial dissection. The accessory lead from the right ventricle displays relatively minor T-wave changes. Fig. 4 shows the electrocardiographic changes that appeared during a five-minute period of subtotal occlusion and during an immediate subsequent period in which the subtotal occlusion was made complete for ninety seconds. The experiment was carried out on Dog 3 several minutes after completion of the experiment shown in Fig. 3. A comparison of Fig. 4 with Fig. 3 shows, therefore, the nature of alterations of the ischemia-injury pattern produced by a complete, ninety-second occlusion with and without an immediately preceding period of prolonged ischemia. Evidently, the effects due to complete occlusion are more pronounced and regress more slowly after occlusion ends if the onset of complete occlusion is immediately preceded by a period of subtotal occlusion.

The Effects of Variable Subtotal Occlusion.—The curves shown in Figs. 5, 6, and 7 represent the effects produced by high-grade subtotal occlusion of five minutes' duration, during which the tension on the ligature was relaxed slightly whenever a definite injury effect appeared in the moving shadow of the galvanometer string. At the end of the five-minute period of subtotal occlusion, the occlusion was made complete for ninety seconds (see time signals in Figs. 6 and 7), after which complete release of the ligature was followed by a return of the curve to a nearly normal form. The accessory lead selected for the preparation (Dog 9) was standard Lead I. The ischemia-injury effects in Lead I, although much smaller in magnitude, are like in kind to those observed in the unipolar lead. Moreover, the order of appearance and disappearance of the changes is the same in the two methods of leading. On the other hand, the time of appearance and disappearance of the changes in the extremity lead, as compared with homologous changes in the unipolar lead, is not in close agreement because effects which have reached striking proportions in the latter are concurrently insignificant in the former type of lead. Other evidence (to be reported later) demonstrates emphatically the unreliability of extremity leads in experiments of the kind under consideration.

<center>DISCUSSION</center>

In 1931, Wood and Wolferth[2] produced brief, complete occlusions of the coronary arteries in dogs and recorded the effects intermittantly with extremity leads. Occasionally, Lead II was recorded continuously.

Certain of their observations and interpretations differ from ours. They observed that the "results of clamping a large coronary become apparent in 15 sec." Unipolar leads demonstrate that the associated electrical changes commence almost at once. They observed further that "occlusion in a healthy fresh heart does not produce electrocardiographic changes as readily (promptly) as it does in a damaged one." We find that the ischemic changes appear immediately, whether or not temporary occlusion (or occlusions) has been previously carried out. They state that "sometimes the experimental occlusion of a large
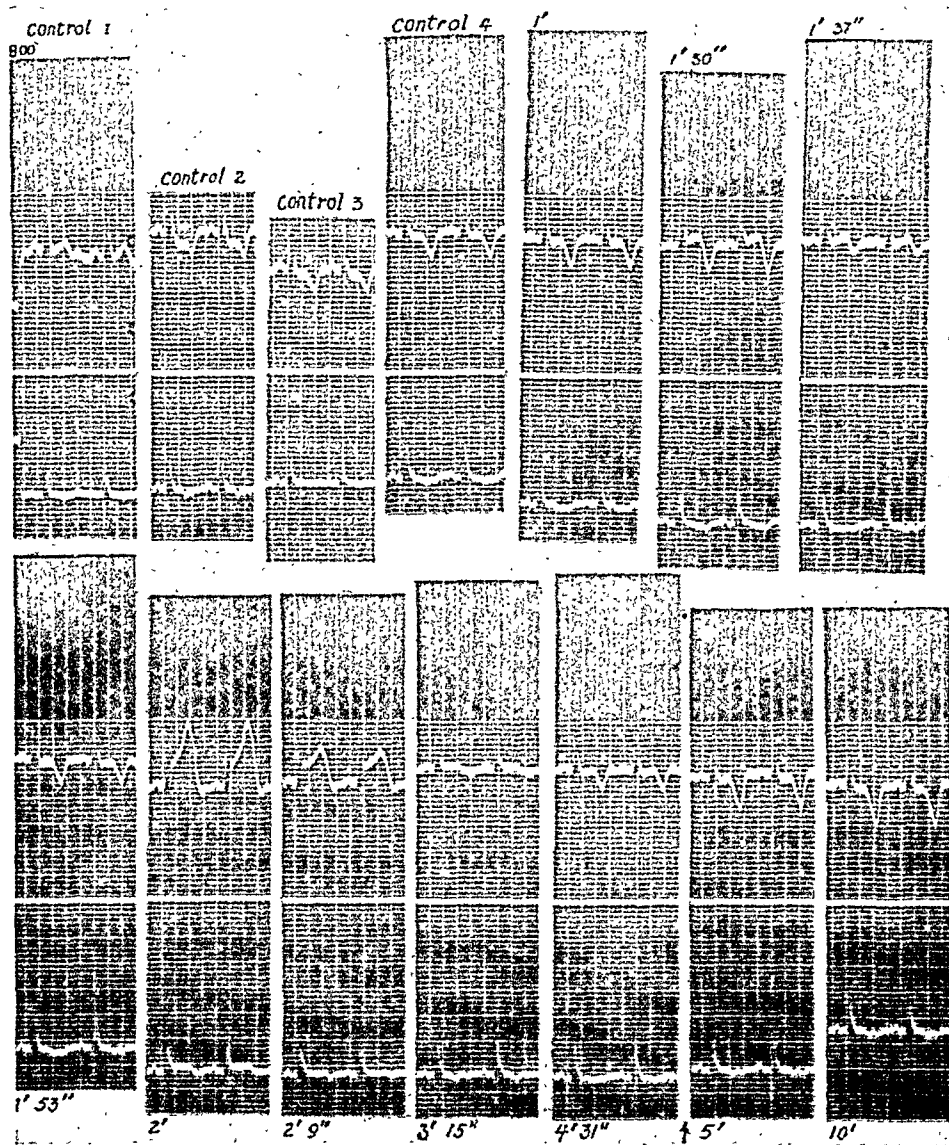
Fig. 5.—The effects of high-grade subtotal occlusion of varying degree for a five-minute period, followed by complete occlusion for ninety seconds. Reading from left to right and from above down: The exploring electrode of the main (upper) lead was on the pericardial sac superjacent to that part of the free wall of the left ventricle normally irrigated by the dissected artery. The accessory (lower) lead is standard Lead I. Controls 1, 2, 3, and 4 are before opening the chest, after opening the chest, after arterial dissection, after warming the pericardium with normal saline, and before occlusion, respectively. The first arrow indicates the interval within which subtotal occlusion was started. The second arrow indicates the interval within which the subtotal occlusion was made complete and during which the continuous strip shown in Figs. 6 and 7 was recorded. The time signal (strip a, Fig. 6) indicates the onset of complete occlusion. The time signal (strip e, Fig. 7) indicates the end of occlusion. The figures over the strips (top row) and under the strips (bottom row) indicate, respectively, the time after subtotal occlusion started, and the time after total occlusion ended. The dash indicates minutes, and the double dash indicates seconds. Standardization is ½ normal and normal for the unipolar and for the extremity lead, respectively. See text.

Fig. 7.—See legend of Fig. 5.

coronary artery . . . caused no change in the (extremity-lead) electrocardiogram.'' We assert that properly placed unipolar leads will invariably show striking electrocardiographic changes of a highly predictable kind when a large coronary artery is suddenly occluded. They state that ''change in the position of the heart was not a factor in these electrocardiographic changes.'' When a unipolar method of leading is employed, in which an exploring electrode is placed on the pericardial sac (or on the heart's surface) superjacent to the tributaries of the occluded artery, it may be safely asserted that the position of the heart is not an influential factor in the kind or magnitude of the electrocardiographic changes associated with the occlusion. On the other hand, we suggest that, when using the extremity leads, the position of the heart may well account for the total absence, the presence, and the direction, singly or in combination, of electrocardiographic changes associated with experimental coronary artery occlusion. Finally, we are able to confirm the major conclusion reached by Wood and Wolferth,[3] namely, that brief coronary artery occlusion is associated with local myocardial changes of slightly longer duration, which are in turn responsible for temporary alterations in the T wave and in the RS-T junction. Our previous [1, 2] and present investigations have attempted to extend the solution of the problem.

It has been shown experimentally,[1] and is now re-emphasized, that the electrocardiographic effects of ischemia precede those of injury, and that this order of appearance is necessarily the same as would occur with myocardial infarction had the latter been permitted to develop by prolonging the occlusion.[*] Since the duration (ninety seconds, or less) of the occlusion usually produced is about one-twelfth as long as that required to produce minimal pathologic changes,[4] it is clear that the electrical phenomena are entirely independent of demonstrable pathologic changes. Consequently, the ischemia-injury changes, although often associated with infarction in man, are not to be regarded as diagnostic of infarction. In contrast are certain well-recognized, permanent QRS changes which are diagnostic of infarction in man and dog, but which are not observed in the ischemia-injury patterns of brief coronary artery occlusions.

It has been shown elsewhere[2] that the ischemia-injury pattern may be interrupted at any desired stage of its development by terminating the complete occlusion, after which the pattern promptly returns to its control form. It has also been shown[2] that a preparation which yields patterns of the negative T variety may be made to yield patterns of the positive T variety by the administration of theophylline with ethylenediamine. In the present experiments it was demonstrated that the ischemia phase may be produced gradually, in stages, by increasing degrees of subtotal occlusion, and that it can be prolonged in proportion to the duration of subtotal occlusion. After release of

[*]The same order of appearance may likewise hold for acute pericarditis.

the subtotal occlusion, the T wave gradually reverts to its original form.   Finally, it is shown that variable, high-grade occlusion is attended with a variable pattern which moves from the ischemia phase into, and out of, the injury phase, depending upon whether the grade of occlusion is increased or decreased.

The kind of electrocardiographic changes produced by the various kinds of arterial occlusion have occurred repeatedly in a highly predictable manner for an over-all total of twenty dogs, upon each of which an average of four occlusive procedures have been carried out. The evidence, so it seems to us, indicates clearly that a second-to-second relationship exists between the electrical activity (ischemia and injury) produced by the involved myocardium and the quantity (or lack) of arterial blood received; that is, the rate at which the electrical effects change is a rough measure of the rate at which the arterial circulation is impaired or improved for as long a time as the involved muscle is able to respond.

Physiologic Considerations.—Little is to be gained at this time by attempting an analysis of the ischemia-injury pattern.   Certain of the broad analytical aspects of comparable electrocardiographic changes in man have been presented elsewhere,[5] and we see no reason why a similar approach is not altogether suitable to homologous electrocardiographic changes in the dog.   The diagrams in Fig. 8*b* will serve our present purpose.   Let the surface of the paper represent that part of the epicardial surface of the heart which is superjacent to the region of the ventricular wall and is normally irrigated by the dissected artery.   At *O* the surface is normal. and complete occlusion has just commenced.   At *1* the exploring electrode is shown in the general vicinity of the center of the surface under consideration, in which there has now appeared a small zone of ischemia.   Within a second after the onset of occlusion the zone of ischemia will have expanded beyond the electrode tip, and the ischemia phase of the pattern will have commenced (strips *a* and *b*, Fig. 6).   In *2* the zone of ischemia is beyond the electrode and the zone of injury is now apparent.   In about forty seconds the zone of injury will have reached the electrode. Concurrently, the transition from the ischemia phase into the injury phase takes place (strips *b* and *c*, Fig. 6).   At *3* the electrode is shown on the injury zone (about fifty-five seconds after the onset of occlusion), and the injury phase of the pattern is well developed (strip *d*, Fig. 7).   Concurrently, the center of the injured zone displays a new kind of activity, possibly because of local release of potassium from the interior of the injured cells.[6]   At *4* the (?K) zone involves the electrode, and the "waterfall" T waves are converted gradually into upwardly directed spikes (within sixty seconds after the onset of occlusion).   If the occlusion is now suddenly released, the zones rapidly vanish in the reverse order to that in which they appeared (strip *e* and *f*, Fig. 7).   If the occlusion is maintained for ten minutes or longer, the initial effect of the (?K) zone gradually vanishes.   Presumably, the
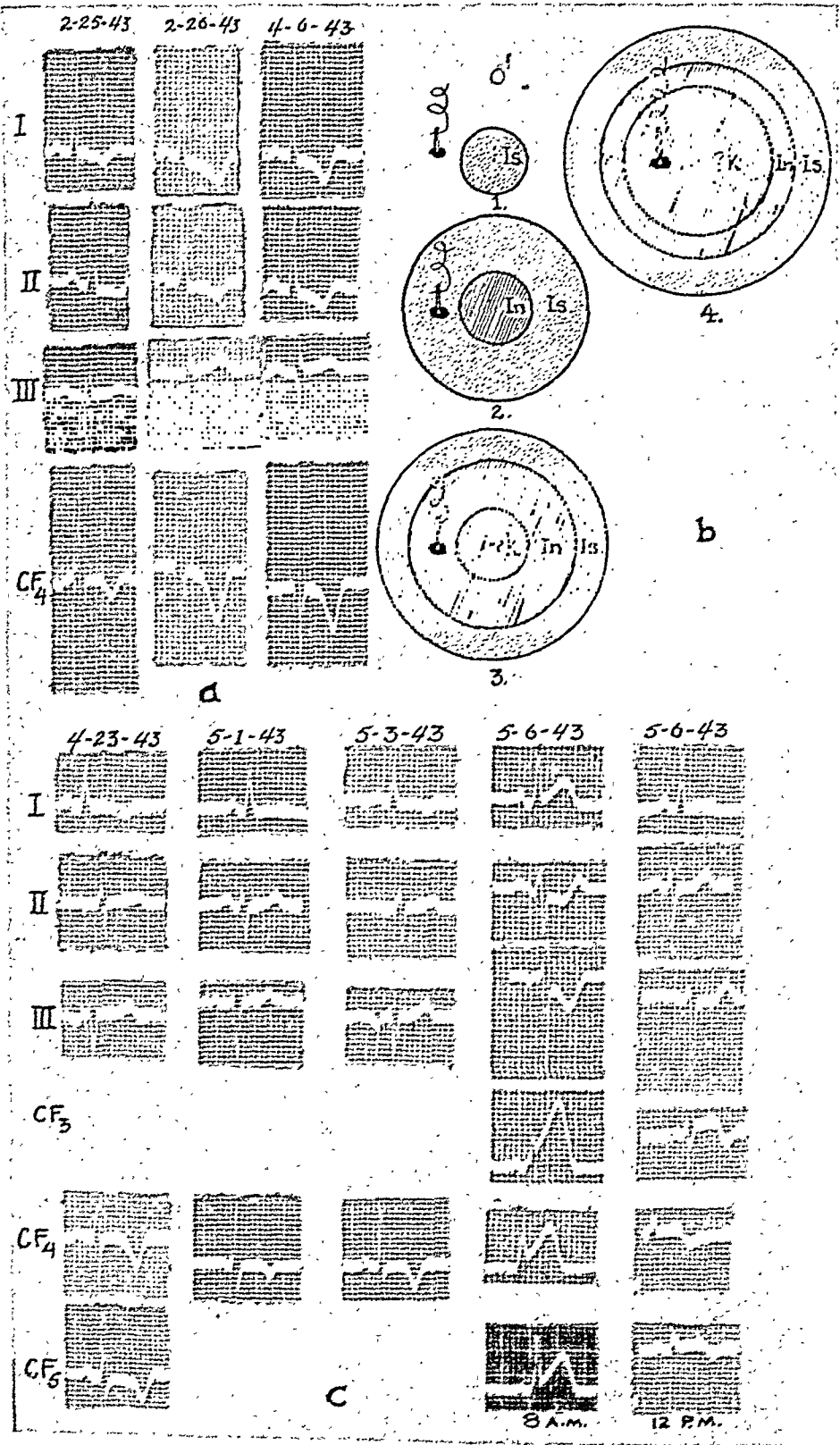
Fig. 8.—(For legend see opposite page.)

action of potassium on the injured zone changes, or the injured zone is no longer able to respond in the same way. The effects of more prolonged occlusion are beyond the limits of this communication.

We wish to emphasize that the cardiac muscle of both man[7] and dog[1] ordinarily passes into and out of the injured state through a stage evidenced by primary T-wave changes and called the ischemia phase. It is our present opinion that the injured zone cannot long endure without local death of most of its central region. On the other hand, the ischemia stage is known to exist in man for at least two weeks without the development of detectable microscopic changes.[7]

Clinical Implications.—If infarction can be prevented or minimized at its *impending* stage, the recognition of this stage will be extremely important clinically. At present, the only possible means of recognition in the impending stage is, so far as we know, the proper evaluation of electrocardiograms which display evidence of acute, local, ventricular ischemia.[5,7] The serial electrocardiograms shown in Fig. 8a and 8c are two examples of the appearance of acute local ventricular ischemia which later developed into the injury stage and infarction. The latter appeared one day after the discovery of acute local ischemia in one patient (Fig. 8a), and within twelve days in the other (Fig. 8c).

SUMMARY

1. When the dog's coronary artery is completely occluded for ninety seconds, an essentially unipolar lead, taken with the exploring electrode superjacent to that part of the myocardium which is ordinarily irrigated by the artery, undergoes a highly predictable sequence of changes.

2. The pattern thus obtained has been referred to as the ischemia-injury pattern.[1,2] The ischemia phase commences almost at once, consists of a primary T-wave change, and lasts from thirty to forty-five seconds.

3. The ischemia phase may be induced gradually, in stages, by subtotal occlusion, the degree of which is increased in a like number of stages. If the subtotal occlusion is promptly ended, the induced T-wave change gradually vanishes.

Fig. 8.—*a*, Three serial electrocardiograms recorded before, during, and after myocardial infarction in a white man, aged 67 years. The curve of Feb. 2, 1943, is interpreted as indicating acute, local ischemia of the ventricular muscle ordinarily irrigated by the left coronary artery. The permanent QRS changes in Lead III of the two subsequent curves indicate "posterior" infarction "'at a distance." Cardiac pain was present only at the time of the first recording. The patient had hypertensive arteriosclerotic heart disease. Fever and an increased sedimentation rate developed on Feb. 26, 1943. No leucocytosis or fall of blood pressure occurred.

b, A diagram of the ischemia-injury distribution under development. See text and Figs. 6 and 7.

c, Serial electrocardiograms recorded from a white woman before, during, and after the development of anterolateral infarction. Repeated, fifteen-minute attacks of cardiac pain had occurred for six days prior to Apr. 23, 1943. No further pain occurred until the morning of May 6, 1943, at which time she experienced a most severe four-hour attack. The first three recordings indicate (under the circumstances) acute local ventricular ischemia of varying intensity in the muscle ordinarily irrigated by the left coronary artery. The permanent QRS changes in the last two recordings indicate myocardial infarction. The curve at 8 A.M. shows the (?K) effect. See text.

4. The ischemia phase may be induced almost at once by subtotal occlusion, and its duration is directly proportional to the duration of the subtotal occlusion. A variable, high-grade, subtotal occlusion causes the pattern to evolve from the ischemia phase into and out of the injury phase, depending upon whether the subtotal occlusion is increased or decreased.

5. A brief description of the distribution upon the epicardial surface of the development and the decay of ischemia and injury is offered, and it is pointed out that the analytical approach presented elsewhere for the analogous electrical problem encountered in man[5] appears altogether suitable for the situation encountered in the dog.

6. It is important to know how long local ischemia, associated with only primary T-wave changes, must exist in order to be followed by local myocardial fibrosis. This we have not ascertained, but analogous changes have been known to exist in man for at least two weeks without detectable myocardial change.[7] Serial electrocardiograms recorded from man are presented, in which the ischemia phase gradually evolved into the injury phase and myocardial infarction. It is emphasized that, if a method is developed by which infarction may be prevented or minimized when treated in its impending stage, the recognition of this stage will be of considerable clinical importance. So far as we know, the only means by which the stage of impending myocardial infarction may be recognized is by proper evaluation of electrocardiograms which display evidence of acute, local, ventricular ischemia.[5, 7]

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OBSERVATIONS ON THE HEART SIZE OF NATIVES LIVING AT HIGH ALTITUDES

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I T HAS been demonstrated by several workers that severe, acute anoxia may cause dilatation of the heart. The effects of chronic anoxia on the heart are, however, by no means clear. There is some experimental evidence to suggest that cardiac hypertrophy may result from prolonged exposure to low concentrations of oxygen. As Van Liere[1] points out, however, there is little or no information in the literature on the heart size of people who live at high altitudes.

During the course of a three-year stay in the Andes, an opportunity was afforded for making observations on this subject. The most useful and accurate information would, of course, have been obtained from autopsies on persons who died from accidents or diseases which are known not to cause cardiac hypertrophy. However, local conditions were not favorable to gathering together a sufficient number of these for study. It was therefore decided to utilize roentgenograms in an attempt to ascertain whether living at a high altitude does cause cardiac enlargement.

MATERIAL AND METHOD

The subjects were normal native Peruvian males of Indian race with a small admixture of white blood in some cases. All had been born at altitudes varying from 10,000 to 15,000 feet, and, with a few exceptions, had lived all their lives at these altitudes. Some had made trips to lower levels or even to the seacoast, but usually not for more than a few months. These men were either applying for work in the smelter or mines or were anxious to leave the company employ.

Their ages ranged from 17 to 66 years. It was recognized that in some cases his exact age was unknown to the man himself, but it is unlikely that the individual discrepancy amounted to more than a couple of years, and, in a large series, the errors would tend to cancel out.

In each case the height was measured in centimeters and the weight in kilograms. An attempt was made to obtain a history of previous illnesses, although the value of the answers was frequently doubtful. A complete physical examination was done, including measurement of the blood pressure and testing of the urine for albumin.

Those who were suffering from detectable cardiac disease were excluded from the study. Electrocardiograms were not taken routinely, but, when an abnormality was found, the case was not included. Cases of hypertension (with a pressure of more than 140/90), thyroid disease, albuminuria, and tuberculosis were eliminated, as were cases of suspected illness in which a definite diagnosis could not be made in the time

available. Special care was taken to rule out pulmonary disease, particularly pneumoconiosis. Among the older subjects it was, of course, not possible to exclude all cases of asymptomatic coronary disease, but it is not likely that any considerable number of these was used.

The roentgenograms were taken at a distance of 6 feet, and the exposure time was $\frac{1}{20}$ second. Exposures were made in the postero-anterior direction at the end of normal inspiration. Consideration was given to the use of lateral views in an attempt to estimate the heart volume by means of a formula such as the Rohrer-Kahlstorf, but the defects of any such formula seemed too great to justify the expense and time involved.

The transverse, long, and broad diameters were measured in the usual way. The frontal area was estimated from the long and broad diameters by means of the nomogram of Ungerleider and Gubner.[2] The estimate of the effect of altitude on heart size was based on the transverse diameter and the frontal area. The imperfections of these two measurements, particularly in borderline cases of enlargement, are too well known to require discussion. Criticism of their shortcomings is, however, applicable chiefly in the individual case, particularly when only one set of figures is available. The objections are much less applicable to a large number of cases such as this series.

The ideal method of ascertaining the effect of high altitude on heart size would have been to compare these data with those derived from normal Peruvian Indian inhabitants at sea level. Since figures for the latter were not available, it was decided to compare the measurements with the normal standards for white persons living near sea level, recently published by Ungerleider and Clark[3] and Ungerleider and Gubner.[2] The possible objections to this procedure will be discussed later.

From the nomograms of Ungerleider and Gubner,[2] the predicted "normal" transverse diameters and frontal areas were ascertained for these natives on the basis of their heights and weights, and these were compared with the actual observations. As an indication of deviation from the standards it was decided to use the percentage changes above or below the "normal" predictions as the raw data, rather than the actual differences. These percentage changes were calculated to the nearest whole figure, for it was felt that the use of decimal places was not justified. The information thus obtained was subjected to statistical analysis.

<center>RESULTS</center>

In all, 273 persons were regarded as suitable for analysis. This sample of the population was unselected with the exceptions noted above, i.e., the exclusion of those suffering from diagnosable disease.

The average height of these subjects was 156.26 cm., and the average weight, 55.63 kg.

Transverse Diameter.—The percentage variations from the predicted "normals" were divided into ten groups of 5 per cent each, ranging from −10 per cent to +35 per cent. The number and percentage of the total are shown in Table I.

A histogram showing the distribution of these cases is presented in Fig. 1.

Fig. 2 shows the frequency distribution curve of these same cases, together with the distribution curve of the 1,460 white persons who

formed the basic data of Ungerleider and Clark's tables.[3] For more accurate comparison the grouping in this series was abandoned, and, to provide a curve of comparable size, the number of cases in each percentage was multiplied by approximately 5.4. Only the smoothed curve of Ungerleider and Clark is shown; the actual numbers of my series are plotted, and an approximate curve is drawn through these. The table and figures show that the transverse cardiac diameters of these natives were definitely greater than the normal standards for white males. The average percentage change in transverse diameter (T. D.) for all cases was +11.5 per cent, with a standard deviation of 7.1; the standard error of the latter was 0.30.

Percentage Change in Transverse Diameter.
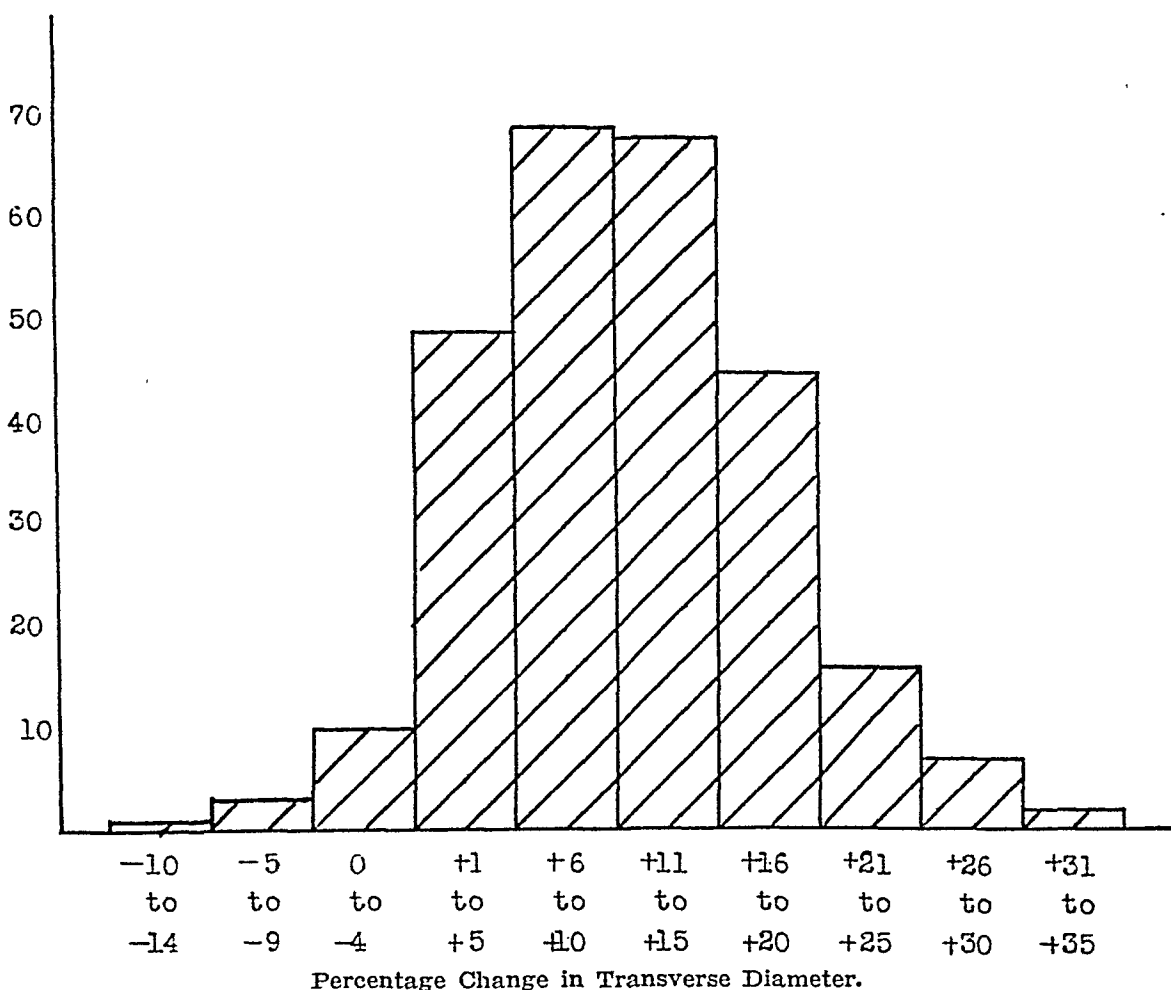
Fig. 1.—Histogram showing the frequency distribution of cases for varying percentage changes in transverse diameter.

TABLE I

PERCENTAGE CHANGE IN TRANSVERSE DIAMETER	-10 TO -14	-5 TO -9	0 TO -4	+1 TO +5	+6 TO +10	+11 TO +15	+16 TO +20	+21 TO +25	+26 TO +30	+31 TO +35
Number of cases	1	3	10	49	69	68	45	16	10	2
Percentage of total	0.37	1.1	3.6	18.0	25.3	24.9	16.5	5.9	3.6	0.73

Comparison of the frequency distribution curves in Fig. 2 suggests that this is at least as valid a sample of the population as is that of Ungerleider and Clark.[2] It is obvious that the range of measurements is significantly shifted to the right, and that the values are definitely higher.

Table II shows an analysis of the influence of age on the percentage change in transverse diameter. If one uses an increase of 10 per cent, or more, over the predicted "normal" as an indication of "enlargement," one can then ascertain the number in each age group who have "enlargment" according to the standards for white males. The average percentage change in transverse diameter for each age group is also shown.

TABLE II

AGE GROUPS	UP TO 19 YR.	20 TO 24 YR.	25 TO 29 YR.	30 TO 34 YR.	35 TO 39 YR.	40 TO 44 YR.	45 YR. AND OVER
Number of cases	25	43	81	52	35	20	17
Number with increase in T.D. of +10 per cent or more	6	20	44	27	26	13	15
Percentage with increase in T.D. of +10 per cent or more	24	47	53	55	74	65	88
Average percentage change in T.D. in all cases	+6.4	+11.3	+10.7	+11.1	+13.9	+12.0	+18.2

The percentage of those with "enlargement" in each group appears at a glance to show a rise with advancing age. On applying the chi square test to these figures, one finds that p is just greater than 0.05. This is about the value of p which is usually taken to be of significance; such a series of figures would be encountered by chance only about once in twenty samples. This point will be discussed later in connection with the results on frontal areas. Except at the extremes of the age groups, there is an insignificant variation in the average percentage increase in transverse diameter. The chi square test gives a value of $p = 0.37$, so that such a set of results could easily arise by chance.

Table III shows the average percentage increase in the transverse diameter for the various predicted "normals," which have been grouped into seven classes. In the five classes containing sufficient numbers for comparison, there is no significant variation in the average percentage change.

TABLE III

PREDICTED "NORMAL" T.D.	10.5 TO 10.9	11.0 TO 11.4	11.5 TO 11.9	12.0 TO 12.4	12.5 TO 12.9	13.0 TO 13.4	13.5 TO 13.9
Number of cases	2	29	103	89	41	8	1
Average percentage change	+24.5	+10.6	+10.0	+11.7	+11.5	+11.1	+2.0

Likewise, as seen in Table IV, the subject's surface area had no influence on the average percentage change in transverse diameter.

The data on the broad and long diameters were not analyzed separately, but the average broad diameter (10.52 cm.) was 20.9 per cent less than the average transverse (13.30 cm.). The average long diameter (14.19 cm.) was 6.7 per cent greater than the average transverse diameter.
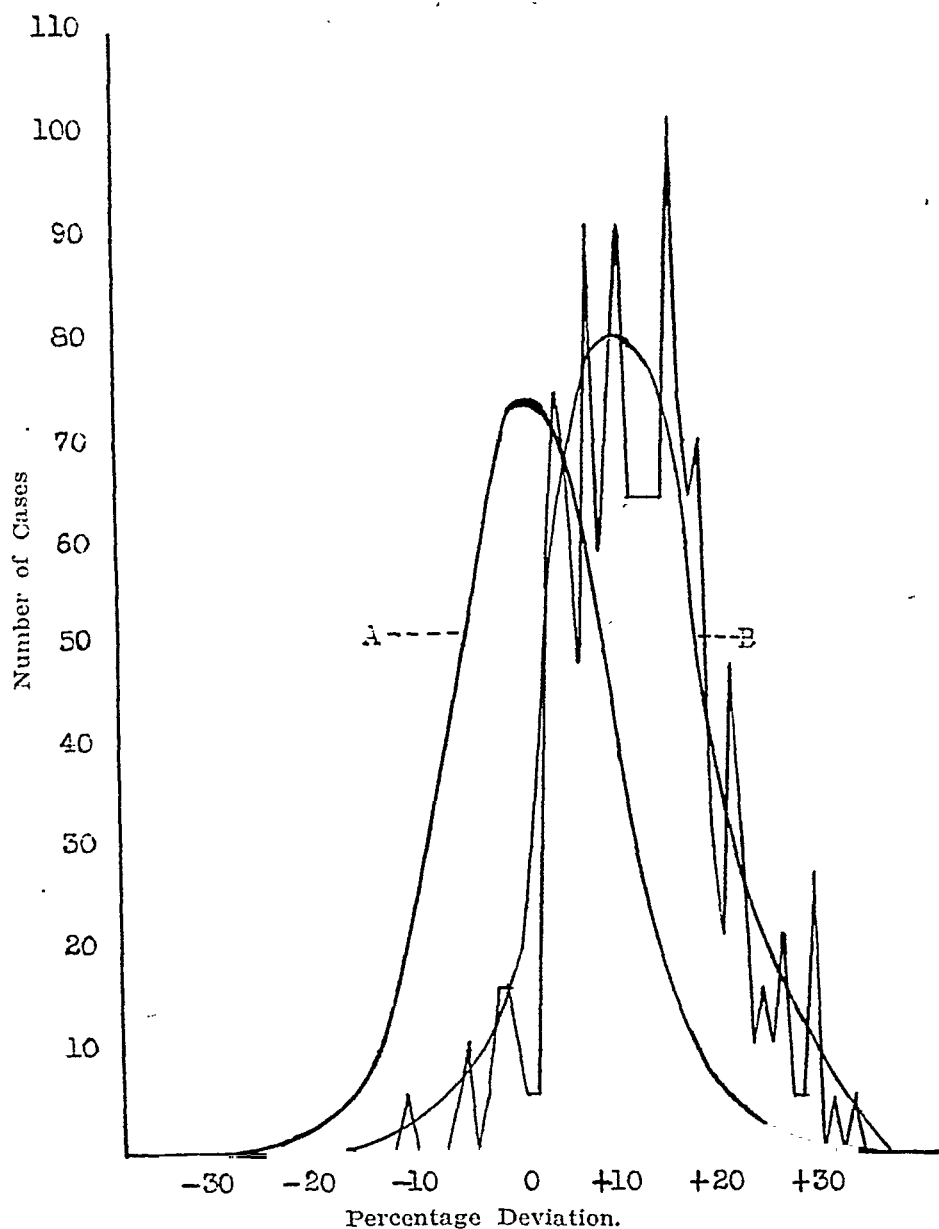
Fig. 2.—A, Smoothed curve of Ungerleider and Gubner's[2] 1,460 cases, forming the normal standards (the plotting of the original data is omitted to avoid confusion in the diagram). B, Curve of the data in this series of 273 cases, multiplied by 5.4 to provide a diagram of comparable size. A smoothed curve derived from this is also shown.

Frontal Area.—The percentage changes in frontal area (F. A.) were divided for convenience into groups of 8 per cent each, ranging from below −16 per cent to over +44 per cent. Table V shows the numbers and percentage of the total in each group. Fig. 3 shows the distribution of these cases.

TABLE IV

SURFACE AREA IN SQ. M.	UP TO 1.40	1.41 TO 1.45	1.46 TO 1.50	1.51 TO 1.55	1.56 TO 1.60	1.61 TO 1.65	1.66 TO 1.70	1.71 AND OVER
Number of cases	17	25	57	61	57	28	18	10
Average percentage change in T.D.	+13.8	+13.4	+9.9	+11.8	+11.1	+10.7	+11.1	+9.7

TABLE V

PERCENTAGE CHANGE IN FRONTAL AREA	UP TO -16	-8 TO -15	0 TO -7	+1 TO +8	+9 TO +16	+17 TO +24	+25 TO +32	+33 TO +40	+41 TO +48	+49 AND OVER
Number of cases	1	9	24	50	61	58	37	15	9	9
Percentage of total	0.37	3.3	8.8	18.3	22.3	21.2	13.5	5.5	3.3	3.3

Here, as in the case of the transverse diameter, there is a definite increase in the frontal area over the normal for sea level inhabitants. No frequency distribution curve on frontal areas of normal whites was available for comparison with these data. The average percentage change in frontal area was +16.3 per cent, with a rather large standard deviation of 14.4; the standard error of the latter was 0.61.

Table VI shows the influence of age on the percentage variations in frontal area; this is analyzed in a fashion similar to that of Table II for transverse diameters. Inspection does not suggest that there is a significantly increasing "enlargement" with advancing age within the limits of the groups studied. This is borne out by the chi square test, which gives a p of 0.60.

TABLE VI

AGE GROUPS	UP TO 19 YR.	20 TO 24 YR.	25 TO 29 YR.	30 TO 34 YR.	35 TO 39 YR.	40 TO 44 YR.	45 YR. AND OVER
Number of cases	25	43	81	52	35	20	17
Number with increase in F. A. of +10 per cent or more	9	32	52	34	24	12	13
Percentage with increase in F. A. of +10 per cent or more	36	74	65	65	69	60	76
Average percentage change in F. A. in all cases	+6.8	+16.0	+17.0	+18.2	+18.5	+18.4	+14.9

TABLE VII

PREDICTED "NORMAL" F. A.	UP TO 87	88 TO 90	91 TO 93	94 TO 96	97 TO 99	100 TO 102	103 TO 105	106 TO 108	109 TO 111	112 AND OVER
Number of cases	5	14	16	30	56	43	48	28	21	12
Average percentage change	+31.6	+25.0	+22.5	+19.8	+13.8	+16.7	+14.1	+12.1	+11.7	+10.5

In Table VII the predicted frontal areas have been divided into ten groups, and for each the number of cases is shown, along with the average percentage change. There is an obvious downward trend in the percentage variation, with increasingly larger predicted "normal" frontal areas. This impression is supported by the chi square test, in which p is less than 0.01; this is strong evidence that this result is not due to sampling error.
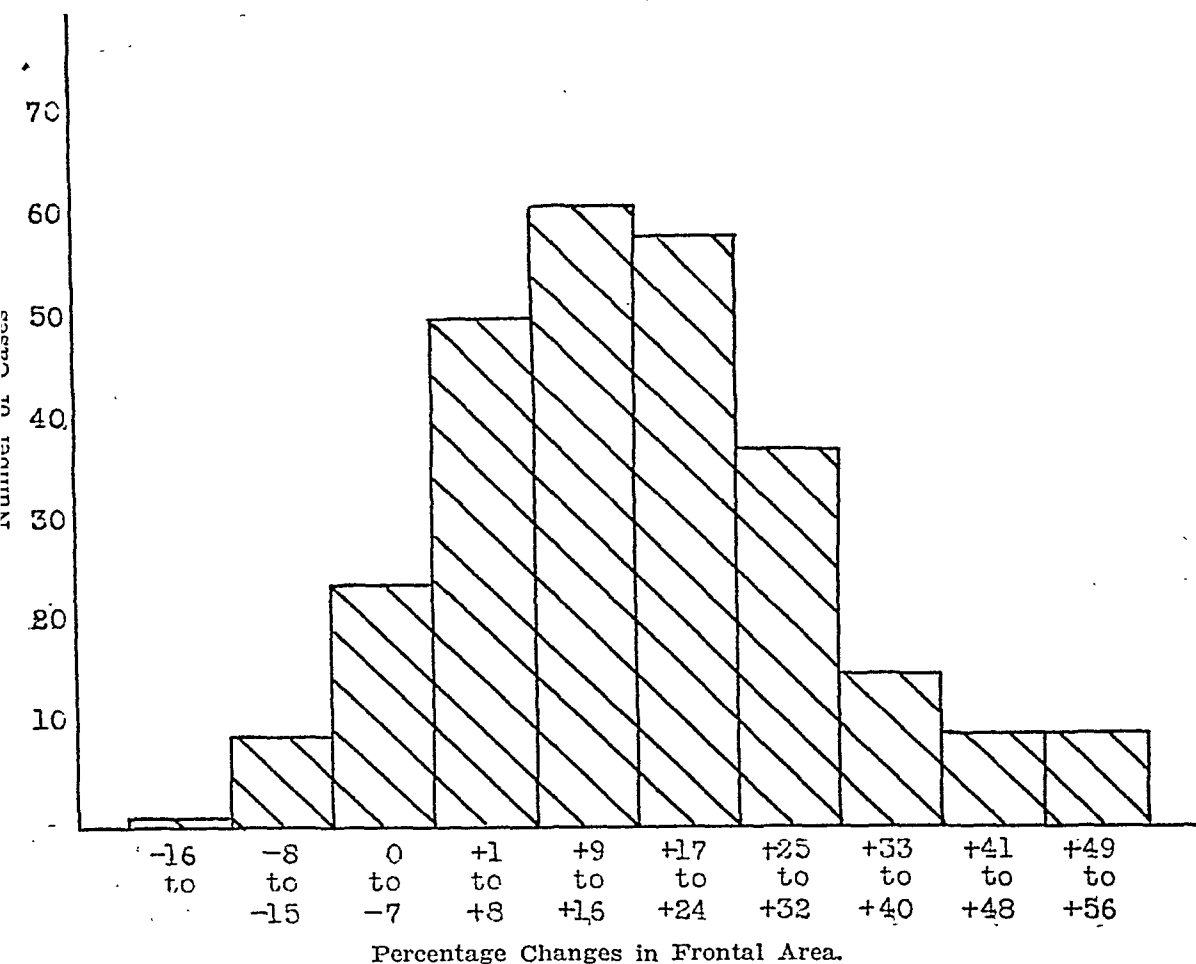
Fig. 3.—Histogram showing the frequency distribution of cases according to varying percentage changes in frontal area.

Table VIII shows the variation in percentage changes in frontal area for different surface areas. The chi square test reveals a p of 0.7, which suggests that the variations are a matter of chance.

TABLE VIII

SURFACE AREA IN SQ. M.	UP TO 1.40	1.41 TO 1.45	1.46 TO 1.50	1.51 TO 1.55	1.56 TO 1.60	1.61 TO 1.65	1.66 TO 1.70	1.71 AND OVER
Number of cases	17	25	57	61	57	28	18	10
Average percentage change in F. A.	+20.4	+23.2	+15.5	+15.8	+15.1	+13.3	+16.6	+14.8

<center>DISCUSSION</center>

As previously pointed out, a comparison of the heart sizes of high altitude inhabitants with those of a population similar in every respect, but living near sea level, would be a desirable method of ascertaining the effect of chronic anoxia on the heart. However, under the circumstances, the measurements obtained had to be compared with those of normal white males. This procedure is open to the obvious objection that the two groups differ in more respects than merely the altitude at which they live. They differ in race, amount and type of work and exercise, nutritional status, and in other respects. It is not known exactly what influence these factors may have, but it is unlikely that many of them have a significant effect on cardiac size. The most serious error may well lie in our inability to take purely racial variations into account.

Anthropometric studies on Indians have concerned themselves largely with external and skeletal measurements, and I am not aware of any data on the sizes and weights of internal organs. It appears probable that there is little variation other than the individual differences which are common to all races. That the Peruvian Indians used in this study are among the smaller Indian tribes of America can be seen from a comparison of their average height with the tables of average statures for various tribes given by Steggerda.[4] In this respect they are similar to the tribes of Southern Mexico and Central America, such as the Mayas. It is worthy of note that the ranges of stature among Indian tribes are comparable to those of various white groups.[4] One may, therefore, suggest that individual height and weight differences,[*] which are here taken into account, are of much greater importance in determining heart size than are racial differences. This view is supported by Comeau and White,[5] who state: "The conclusion is reached that heart size in normal individuals is dependent principally on body build, and that genetic, racial, and environmental factors are usually important chiefly as they affect body structure."

The observations reported here show that the heart size, as measured by the transverse diameter and frontal area, is significantly greater among native residents of high altitudes than among white persons living near sea level. One cannot dogmatically assert, for the reasons given, that chronic anoxia is the causative factor, but it seems to be a reasonable explanation.

The following questions logically arise: Is this "enlargement" an inherited and permanent characteristic, or does it begin in infancy or childhood? Does it increase progressively throughout life, or even reach a certain degree and then cease? The figures available do not provide a definite answer because of lack of data on younger subjects.

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[*]Ungerleider and Clark[3] concluded that, although short men have an average transverse diameter of the heart which is 1 or 2 mm. greater than that predicted in their tables, the difference was so slight as to make any further correction for height unnecessary.

It is to be noted that both the transverse diameter and frontal area show a smaller average increase in the subjects who were 17 to 19 years old than in subjects at other ages. Whether or not this is significant cannot be decided at present. Application of the chi square test to both sets of figures reveals that this result could well have been a sampling error. If one studies the percentage of cases of "enlargement" at various ages, the chi square test on the figures for transverse diameter is borderline, i.e., we are reaching the point at which chance is unlikely to be the cause. However, the results with frontal areas do not corroborate this. One must conclude that certain evidence of progressive "enlargement" between the ages of 20 and 45 years is lacking.

As might be expected, the subject's surface area had no influence on the changes in heart measurements.

Variations in the predicted "normal" transverse diameter had no effect on the percentage changes which occurred. However, in the case of frontal areas, there was a progressive fall in the average percentage change for increasingly large predicted frontal areas (see Table VII). This result, as indicated above, can scarcely be due to chance, but the explanation for it is obscure.

The results of experimental studies on the effect of low oxygen concentrations on the heart are of some interest. Takeuchi,[6] among others, was able to produce definite cardiac dilatation in cats by having them inhale mixtures of nitrogen and air. It was his impression that a large proportion of the change occurred in the lower degrees of anoxemia. At a blood oxygen saturation of 85 per cent, the heart was much dilated. Hilton and Eichholtz[7] showed that the state of contraction of the coronary vessels was proportional to the oxygen saturation of the blood; a fall of oxyhemoglobin saturation below 20 per cent caused maximal dilatation. While confirming, in general, these results in respect to coronary flow, Gremels and Starling[8] found that the degree of oxygen saturation had no influence on heart volume until it fell to 40 per cent; dilatation then occurred and progressed as the saturation fell to 8.5 per cent. They concluded that, under anoxemia, the heart takes up oxygen by an augmented coronary flow and by an increased coefficient of utilization. In more prolonged experiments, Van Liere[9] demonstrated that, when guinea pigs were exposed to simulated altitudes of 14,000 to 18,000 feet for periods up to 105 days, there was an average increase in the heart weight/body weight ratio of 55.8 per cent.

It is apparent, of course, that the time element is relatively short, and that conclusions drawn from such experiments may not necessarily be applicable to human beings who have been exposed to anoxia for years or even generations.

Results similar to those in animals have been obtained in short term experiments on human beings. Whitney[10] reported that five out of ten men in a low pressure chamber at varying altitudes above 14,000 feet developed cardiac dilatation; in each case, severe symptoms of acute alti-

tude sickness ensued. In carefully controlled experiments, however, Le Wald and Turrell[11] produced no significant change under acute anoxia.

Barcroft and others[12] during the Peru expedition could find no consistent changes in the cardiac diameters of several of the expedition members; in fact, in two cases the heart appeared to be smaller. The observations were too few and not sufficiently controlled for any conclusions to be drawn; no data on high altitude residents were collected. Talbott and Dill[13] reported studies on healthy persons living at 17,500 feet. Roentgenographic facilities were not available, apparently, but in each case it was noted that the heart was not enlarged to percussion. No inferences can be drawn from this for several reasons. Percussion is very likely to mislead, particularly in cases of emphysema, and this was present in five of the six cases studied. Moreover, all of these men had been born in the lowlands of Chile or Bolivia, and had been resident in high altitudes for only two to fourteen years. In our present state of knowledge, one cannot regard them in the strictest sense of the term as "permanent inhabitants," as do Talbott and Dill.

It is perhaps not always remembered that hypertrophy in itself does not contribute the major portion to even a moderate enlargement of the cardiac silhouette. For example, an increase of 1 cm. in the thickness of the left ventricular wall, which, from the pathologist's viewpoint, is respectable, would not necessarily widen the transverse diameter a significant amount. It is therefore reasonable to assume that dilatation is always present when there is enlargement of the heart. In the absence of autopsy data, it is not possible to say how much of the "enlargement" in these cases was due to hypertrophy and how much to dilatation.

The mechanism and significance of this "enlargement" are as yet uncertain. Hill[14] expressed the opinion that cardiac hypertrophy may be an "important means of acclimatization" to high altitudes. Probably the fundamental cause is oxygen lack, and it appears likely that this operates directly on the cardiac muscle, which, at the altitudes in question, is exposed to arterial oxygen saturations of about 80 to 87 per cent. In spite of the adaptive mechanisms by which the cardiac fiber acquires its necessary supply of oxygen, such as a greater amount of circulating hemoglobin, dilatation of the coronary vessels, an increase in the coefficient of oxygen utilization, and perhaps an increase in cardiac muscle hemoglobin (Hurtado, et al.[15]), it is possible that, over long periods of time, these measures are not sufficient. A permanent increase in the length of the cardiac fiber may be necessary to liberate the required energy, and, in time, this would result in hypertrophy. Other factors, such as acceleration of the development of coronary sclerosis, may play a part.

It has been suggested that the increased viscosity of the blood places an added strain on the heart,[16] and might therefore lead to enlargement.

There are at least two serious objections to this theory. Although the blood viscosity of high altitude residents is much increased, the increase is due entirely to the augmented number of erythrocytes; the viscosity of the serum is unchanged. As measured in vitro by an instrument such as the Hess viscosimeter, the viscosity increment is much greater than in vivo, for the flow of the more numerous erythrocytes, which is responsible for the increase, is largely axial in the arterioles (Dill[17]). Moreover, increased viscosity in the systemic circulation could operate only by raising the peripheral resistance and thereby elevating the blood pressure. Hypertension is not unusually frequent among inhabitants of high places.

It is interesting to note that persons suffering from chronic mountain sickness, or Monge's disease, nearly always have abnormally large hearts. This was true in five out of seven of Hurtado's[18] cases. In this disease much emphasis has been placed on the hematologic changes, which, in some respects, resemble those of polycythemia vera. It may be that insufficient attention has been paid to the cardiovascular changes which contribute to the disability and may play an important part in the periodic exacerbations of the disease from which these people suffer.

SUMMARY

A study was made of the cardiac measurements, as ascertained roentgenographically, of 273 normal native Peruvian male residents of high altitudes. The data obtained were compared with the normal predicted values for white persons living near sea level.

As judged by the transverse diameter and frontal area, the size of the cardiac silhouette was definitely greater in these people than in normal white inhabitants of low altitudes. The average increase in transverse diameter was 11.5 per cent, and, in frontal area, 16.3 per cent. In the age groups studied, no progressive enlargement with increasing age was evident.

The possible mechanism and significance of this "enlargement" are discussed. It is suggested that this may be one of a variety of adaptive changes which occur with prolonged exposure to low concentrations of oxygen.

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MYOCARDIAL INFARCTION INDICATED BY ANGINA PECTORIS OF EFFORT OR BY BRIEF ATTACKS OF ANGINA OF REST, WITH REMARKS ON PREMONITORY PAIN

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WHEN the blood supply to the heart muscle becomes inadequate relative to its needs, angina pectoris develops in susceptible persons. Angina of effort ("Heberden's angina") is thought, as a rule, to be associated with a reversible nutritional disturbance. As soon as the demands on the heart are decreased, the anginal pain subsides, and no structural damage to the myocardium results. When, however, relative ischemia is severe and protracted, myocardial infarction takes place, even in the absence of complete occlusion of coronary branches. In typical cases, myocardial infarction is indicated by anginal distress more severe and protracted than that which usually accompanies reversible damage of the myocardium. The pain lasts one hour, or several hours, or even days, and is not relieved by rest or nitroglycerin. It may be associated with profuse perspiration, collapse, nausea, and vomiting. It is followed by fever, leucocytosis, a fall in blood pressure, rapid sedimentation of the erythrocytes, a pericardial friction rub, and progressive electrocardiographic changes.

The outstanding symptom of myocardial infarction that usually calls for medical care is pain of unusual severity and duration. However, there are atypical cases in which the symptom of pain is less characteristic. Atypical features are said to be present in 40 per cent of the cases of myocardial infarction.[1] Anginal pain may be entirely absent, and myocardial infarction be suggested only by the sudden development of congestive heart failure, pulmonary edema, or severe fatigue.[2-7] Painless attacks are infrequent, however. Thorough questioning elicits the fact that there was some kind of anginal pain in the overwhelming majority of cases.[8, 9] A subacute course of myocardial infarction has also been described, without startling manifestations in the beginning, and with vague symptoms and delayed electrocardiographic changes.[10]

In the great majority of atypical cases, myocardial infarction is associated with mild anginal pain or with distress of short duration.[1, 2, 4, 6, 11] Herrick,[4, 9] in his early reports on the clinical manifestations of myocardial infarction, has mentioned the occurrence of mild attacks which, in his opinion, were more frequent and of greater im-

portance than was generally realized. They are deceptive and treacherous, often ignored by patients, and neglected by physicians. The victims frequently overstrain their hearts and succumb to ventricular fibrillation. Herrick stressed the necessity of studying "in what way may the cases be recognized more definitely" and "what are the minimum signs and symptoms" of myocardial infarction.[12] We are still far from having fully answered these questions.

In a study undertaken during the last two years, we have investigated the features of atypical cases of myocardial infarction with special reference to the anginal manifestations. The occurrence, the character and duration, and the precipitating causes of anginal pain were ascertained by painstaking questioning. Each patient was questioned by myself and another physician. Such patients as gave a vague history, or were not intelligent enough to answer questions satisfactorily, were excluded from this study. The present report includes sixteen cases in which clinical and laboratory evidence suggested myocardial infarction, although the anginal manifestations were atypical. No history of a severe, protracted anginal pain of the classical type was obtained. In nine cases anginal pain associated with effort was the main symptom, and there was no angina of rest. In seven other instances the occurrence of myocardial infarction was indicated by brief anginal attacks at rest, lasting but a few minutes, and sometimes even relieved by nitroglycerin. The significant features of the atypical attacks are illustrated in the following case reports.

<div align="center">CASE REPORTS</div>

CASE 1.—J. B., a white man, aged 64 years, in February, 1932, after pushing his car, suffered an attack of severe precordial pain which lasted several hours. Myocardial infarction had then been diagnosed in the Cardiac Clinic. Recovery from this attack was complete, and the patient was able to walk as many as fifty blocks without experiencing discomfort.

Early in March, 1941, while walking on the street, the patient felt a sharp, terrific pain substernally and radiating to the jaw. When he stopped walking the pain subsided. Similar attacks occurred on the following days. Walking a distance of two or three blocks caused pain in the chest. Two electrocardiograms, taken March 11 and 18, 1941 (Fig. 1, A and B), failed to reveal significant changes; but the sedimentation rate (Westergren) was 68 mm. on March 12, 1941, and the leucocyte count was 11,600. The condition improved somewhat in the second half of March; the patient could walk a distance of six or seven blocks without experiencing pain, and the sedimentation rate fell to 36 mm.

In April, 1941, the anginal attacks again became more severe; they occurred even at rest, often at night, and lasted from ten to twenty minutes. They were promptly relieved by nitroglycerin. The patient had 10 to 12 anginal attacks of short duration within twenty-four hours. An electrocardiogram taken April 24, 1941 (Fig. 1, C), showed flattening of T_1, together with an increase in the voltage of T_2. These signs

were interpreted as indicative of myocardial infarction.[13-15]   Also, inversion of the T wave had developed in the precordial lead.   Although strict bed rest was instituted, the patient suffered, on April 30, 1941, a severe attack of protracted anginal pain which required the administration of morphine.   On the following day a pericardial friction rub was heard.   An electrocardiogram taken May 1, 1941 (Fig. 1, D), showed inversion of T_1 and low voltage of QRS in the standard leads. R_4 had disappeared, and the inversion of T_4 was more pronounced. Another violent anginal attack occurred May 10, 1941; it was followed by pulmonary edema, and the patient grew rapidly worse.   An electrocardiogram taken May 12, 1941 (Fig. 1, E), showed a downwardly directed main deflection and elevation of S-T in Lead I; there were also a high take-off of S-T and elevation of T in Lead IV.   The patient died May 22, 1941.

Post-mortem examination revealed marked arteriosclerotic narrowing of the coronary arteries.   The right coronary artery was almost completely occluded by an old thrombus.   The apical region of the left
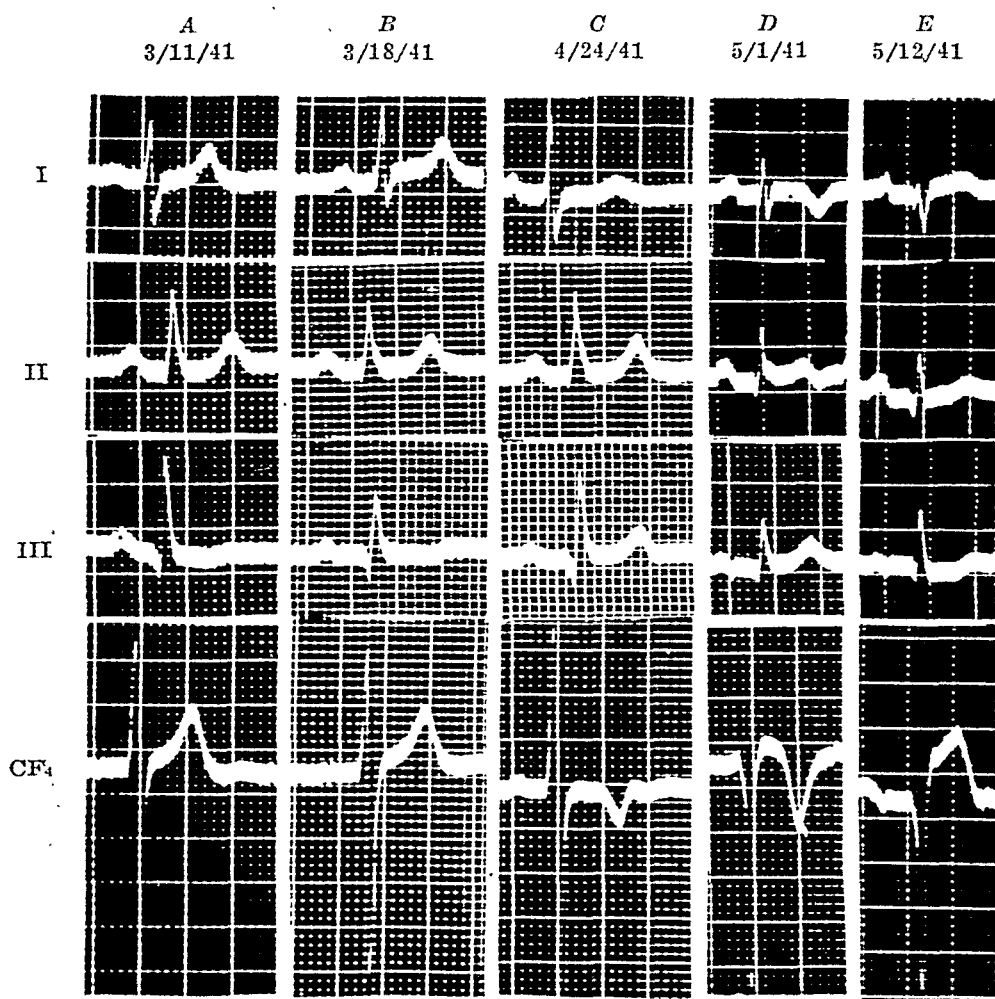
Fig. 1.—Case 1. Severe angina of effort since early in March, 1941. Tracings *A* and *B*, taken March 11 and 18, 1941, showed no significant changes. Numerous brief anginal attacks on rest occurred in April, 1941. Tracing *C*, taken April 24, 1941, showed flattening of T_1, with increase in voltage of T_3: also, inversion of T_4. A new, severe, anginal attack, followed by pericardial friction rub, occurred April 30, 1941. Tracing *D*, taken the next day, showed low voltage of QRS in the standard leads and inversion of T_1. R_4 had disappeared, and inversion of T_4 was even more pronounced. Another severe anginal attack took place May 10, 1941. Tracing *E*, taken after two days, showed a downward main deflection in Lead I. S-T had become slightly elevated and fused with the diphasic T wave in Lead I. The S-T segment was depressed in Lead III. Lead IV showed, besides absence of R, elevation of S-T; T_4 had become upright.

ventricle was thinned, and its muscle replaced by fibrous tissue. In addition, there were large areas of yellowish discoloration, with hemorrhages, indicating recent infarction, in the lateral wall of the left ventricle and in the interventricular septum. Whitish streaks of fibrosis were also visible in the posterior wall of the left ventricle.

Severe angina pectoris of effort and, later, short anginal attacks of rest, relieved by nitroglycerin, preceded the typical attack of myocardial infarction. The initial attacks would readily fit into the designation "premonitory pain," were it not for the increased leucocyte count and sedimentation rate which accompanied the phase of angina of effort, and the electrocardiographic changes during the period of brief anginal attacks of rest. Thus, we are led to believe that the "premonitory pain" indicated the onset of myocardial necrosis in a period of progressive coronary insufficiency which finally culminated in extensive myocardial infarction.

CASE 2.—E. S. was a white woman, aged 52 years. Her father and uncle had died from heart disease in their early fifties. The cardiac complaints of the patient started suddenly on Aug. 1, 1941. While walking, she felt a violent substernal pain which radiated to the right half of the chest and right shoulder and arm. Thereafter she was unable to walk, even slowly, more than one-half block without experiencing pain in the chest. When she rested the pain promptly subsided. No attacks of pain occurred during rest. The patient was first examined in December, 1941. There were no abnormal physical signs. The blood pressure was normal. The sedimentation rate, tested twice during December, 1941, was elevated (55 and 40 mm., respectively). The blood Wassermann reaction was negative. An electrocardiogram taken Dec. 11, 1941 (Fig. 2, A), showed a shallow, inverted T_1, with upright T_2 and T_3. T_4 was sharply inverted. On Dec. 31, 1941, the electrocardiographic changes had partly disappeared (Fig. 2, B). T_1 was upright, but of low voltage, and the inversion of T_4 was less pronounced. After four weeks' rest in bed the condition of the patient had improved little. Walking only one block caused pain and forced the patient to rest. After taking nitroglycerin the patient was able to walk two or three blocks before pain developed.

This patient suffered from angina of effort, and had never experienced pain at rest. The increased sedimentation rate and significant electrocardiographic changes pointed to myocardial infarction. The anginal syndrome which signalized myocardial infarction had two significant features. It had started suddenly; in fact, the patient remembered after five months the exact date when she first experienced pain on effort. And the complaints were of marked severity; pain in the chest was produced by walking a distance of only one-half block.

CASE 3.—M. S. was a white man, aged 66 years. When the patient was first seen in the Cardiac Clinic, on Feb. 20, 1942, he gave a history of anginal complaints of four years' duration. A burning pain was felt substernally when the patient walked fast on level ground, or slowly

uphill; the pain subsided promptly when effort was discontinued. There had never been angina of rest. An electrocardiogram taken Feb. 20, 1942, showed deep Q waves and inversion of T in Leads II and III.

This patient presented a history of angina of effort of four years' duration; he had never experienced anginal pain during rest. The electrocardiogram showed changes that are usually associated with posterior wall infarction.

CASE 10.—H. J. was a white man, aged 52 years. The fact that he had hypertension had been discovered ten years before. Beginning early in 1941, the patient experienced substernal pressure when he walked in the morning. In November, 1941, a subtotal gastrectomy was performed because of gastric ulcer. Two weeks after the operation, while the patient was resting in bed, he suffered an attack of substernal
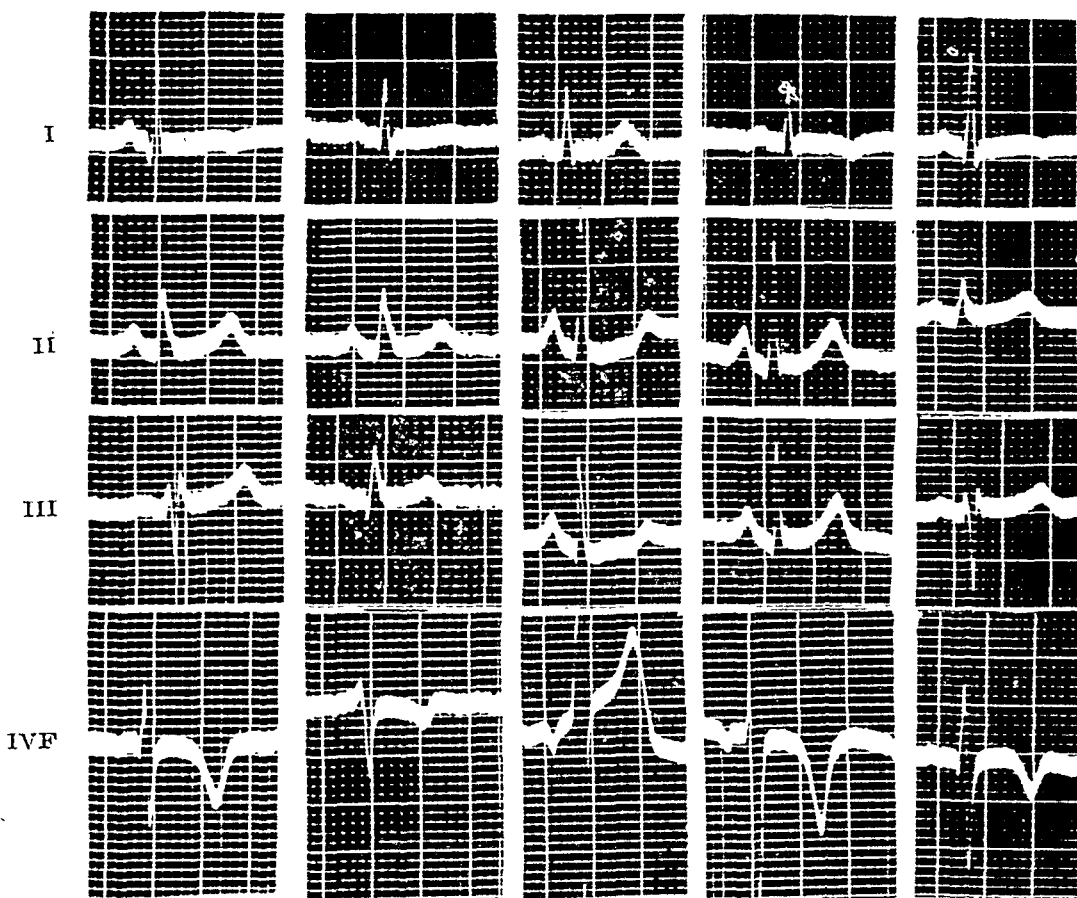
Fig. 2.—Case 2. Severe angina of effort had developed suddenly on Aug. 1, 1941. No angina of rest. Tracing *A*, taken on Dec. 11, 1941, showed a shallow, inverted T_1, with upright T_2 and T_3. T_4 was sharply inverted. *B*. After three weeks, T_1 had become upright, but was still of low voltage, and the inverted T_4 had decreased in voltage.

Case 10. Angina of effort since early in 1941. Gastrectomy was performed Nov. 4, 1941. An attack of substernal pressure of ten minutes' duration occurred Nov. 19, 1941; it was followed by similar attacks on the next few days. Tracing *C* was taken on the day of the first anginal attack. It showed distinct depression of S-T in Leads II and III (without elevation of S-T in Lead I). There was elevation of S-T in Lead IV, and T_4 was upright and of marked amplitude. Tracing *D*, taken seven days later, showed inversion of T_1 and sharp inversion of T_4.

Case 11. Angina pectoris of effort for four months. Two attacks of angina of rest, lasting about fifteen minutes, had occurred six weeks prior to examination. Tracing *E*, taken Aug. 2, 1940, showed convex S-T and late inversion of T in Lead I. There was also sharp inversion of T_4.

pressure with radiation to both arms. The pain was associated with profuse perspiration and lasted ten minutes. Similar attacks followed in the next few days; none lasted longer than ten minutes. Marked weakness developed after these attacks. The temperature rose to 101.4° F. on the day after the first anginal attack. The sedimentation rate, which had been 13 mm. (Westergren) prior to the anginal seizures, increased to 31 mm. on the ninth day, and to 37 mm. on the thirteenth day, after the onset of the anginal attacks. Electrocardiographic examination (Fig. 2, *C* and *D*) revealed progressive changes resulting in inversion of the T waves in Leads I and IV.

This patient, who had suffered from angina of effort for a year, experienced, after an abdominal operation, a few brief anginal attacks while he was at rest, none of which lasted more than ten minutes. The subsequent rise in temperature, increased sedimentation rate, and electrocardiographic changes pointed to myocardial infarction.

CASE 11.—W. L. was a white man, aged 48 years. When he was first seen in the Cardiac Clinic, Aug. 2, 1940, the patient complained of substernal pain, with radiation to the arms, of four months' duration. At the outset the pain was felt on walking and relieved by rest. During the preceding six weeks, however, anginal pain occurred twice at night, and lasted about fifteen minutes. After rest in bed for eight days the nocturnal attacks subsided. An electrocardiogram taken six weeks after the first occurrence of anginal pain of rest (Fig. 2, *E*) showed a convex S-T segment and a shallow, inverted T wave in Lead I, and sharp inversion of T_4.

After a period of angina pectoris of effort of four months' duration, this patient had two anginal attacks during rest, neither of which lasted more than fifteen minutes. The electrocardiographic changes pointed to anterior wall infarction.

The clinical and laboratory data in the cases which were the object of this study are presented in Table I. The cases can be divided into two groups. Group I comprises Cases 1 through 9, in which myocardial infarction was associated with angina of effort. Group II includes Cases 10 through 16, in which evidence of myocardial necrosis was observed after brief attacks of angina of rest. In both groups the presence of myocardial infarction was suggested by fever and leucocytosis or increased sedimentation rate, or by a combination of these signs with anginal manifestations. Significant electrocardiographic changes were observed in all cases but one (Case 1). In the latter, the electrocardiogram was normal during the period of angina of effort, but the sedimentation rate was markedly increased. Significant electrocardiographic changes developed a few weeks later, in association with brief anginal attacks of rest. Finally, there were severe and protracted anginal attacks which were typical of myocardial infarction; necropsy revealed old and recent, extensive myocardial necrosis.

Among the electrocardiographic changes, inversion of T_4 was most frequent (nine cases). It was accompanied by inversion of T_1 in six

cases, and by a flat T_1 in two instances. It must be mentioned that in none of these cases was there electrocardiographic evidence of left ventricular strain; there was no depression of S-T in Lead I, and, when T_1 was inverted, its limbs were symmetrical. In one case, the T wave was inverted in all of the standard leads. A deep Q wave in Leads II and III was observed in four instances. Progressive changes in serial electrocardiograms were noted in four cases.

The electrocardiographic abnormalities and other clinical evidence of myocardial necrosis did not differ essentially in the two groups. Next to the electrocardiogram, the sedimentation rate underwent significant changes most frequently. A rapid sedimentation rate, varying from 21 to 71 mm. (Westergren), was observed in nine cases. Leucocytosis was present in five instances. Rise in temperature was noticed in three cases.

Angina of effort was the outstanding symptom in Group I; brief anginal attacks of rest were the prominent clinical feature in Group II. There was some overlapping of these symptoms, however, in the two groups. In two cases of Group I (Nos. 1 and 4), angina of effort, with laboratory evidence of myocardial necrosis, was followed by angina of rest, and, in one case of Group II (No. 15), angina of rest was preceded, in an interval of a few days, by the sudden development of severe angina of effort.

Angina pectoris of effort, which was the significant symptom in Group I, presented certain characteristics which seem to be essential in the diagnosis of progressive coronary insufficiency and ischemic myocardial necrosis. The onset of pain was often abrupt; one patient (Case 2) remembered the exact date when she had first experienced pain on effort. In another case (No. 6), in which angina of effort had been present for some time, myocardial infarction was accompanied by a sudden increase in the severity of the symptoms. The patient, who formerly had been able to walk three blocks before anginal pain occurred, complained suddenly that walking only one-half block caused severe distress. At the same time, serial electrocardiograms showed progressive changes indicative of anterior wall infarction. In addition to sudden changes in the functional capacity of the heart, the absolute amount of effort which causes anginal pain seems to be of diagnostic importance. Seven patients in Group I reported that walking one-half to three blocks produced angina pectoris. Such greatly diminished coronary reserve, in our experience, is usually associated with recent or past myocardial infarction.

In Group II, anginal attacks at rest were the first anginal manifestation in three cases (Nos. 13, 14, 16). In five instances, the onset of angina of rest was preceded in intervals of one week to twelve months by common angina pectoris of effort. The number of brief attacks of angina of rest which characterized the phase of myocardial necrosis varied from two to twenty; they lasted from a few seconds to twenty

TABLE I

ANALYSIS OF 16 CASES OF ATYPICAL ANGINAL PAIN WITH EVIDENCE SUGGESTIVE OF ISCHEMIC MYOCARDIAL NECROSIS

CASE	AGE	SEX	ANGINAL MANIFESTATIONS	EVIDENCE SUGGESTIVE OF ISCHEMIC MYOCARDIAL NECROSIS	NECROPSY OBSERVATIONS	REMARKS
1. J. B.	64	♂	In 1932, attack of anginal pain diagnosed as myocardial infarction. In March, 1941, sudden onset of severe angina pectoris of effort. In April, 1941, anginal attacks at rest, lasting 10 to 20 minutes, relieved by nitroglycerin. On April 30, 1941, a severe protracted anginal attack, followed by pericardial friction rub. Another severe attack resulted in progressive heart failure and death, on May 22, 1941	In March, 1941, during the period of severe angina of effort, sedimentation rate markedly increased. Leucocytosis. Normal electrocardiograms. In April, 1941, during the period of brief anginal attacks of rest, the electrocardiogram showed flattening of T_1, increase in the voltage of T_2, and inversion of T_4	Fibrosis and thinning of the apical area of the left ventricle. Multiple recent infarctions in the left ventricle due to thrombotic occlusion of the arteriosclerotic ramus descendens anterior of the left coronary artery	
2. E. S.	52	♀	Sudden onset of angina pectoris of effort on Aug. 1, 1941. Patient could not walk one block without experiencing pain. No pain at rest	Sedimentation rate (Westergren), tested twice in December, 1941, was 55 and 40 mm., respectively. Electrocardiogram (on Dec. 11, 1941) showed shallow inversion of T_2 with slightly elevated S-T in Lead I, and sharp inversion of T_4		Father and mother died from heart disease in their fifties
3. M. S.	66	♂	For four years angina pectoris of effort. Never anginal pain on rest	Electrocardiographic changes: deep Q and inverted T in Leads II and III, suggestive of posterior wall infarction		

	Age	Sex			
4. P. S.	52	♂	Sudden onset of angina pectoris of effort in November, 1941. The attacks increased in severity. In February, 1942, a severe anginal attack occurred, lasting one-half hour. Since then frequent pain attacks during rest, all short and relieved by nitroglycerin. Sudden death five months after the onset of anginal complaints	During the period of angina of effort: Sedimentation rate (Westergren) 48 mm. An electrocardiogram showed isoelectric T_1 and sharp inversion of T_4. These changes subsided during the following two months, but the sedimentation rate remained high (67 mm. on March 28, 1942)	Brother died from coronary attack at the age of 55 years. Patient suffered from hypertension
5. J. K.	57	♀	Since second week of February, 1941, severe angina of effort. Walking one block caused precordial pain. No angina of rest	Sedimentation rate (Westergren) on March 21, 1941, was 32 mm. An electrocardiogram taken March 11, 1941, showed isoelectric T_1 and sharp inversion of T_4. After eleven months, when the patient was re-examined and her condition was found improved, a normal electrocardiogram was obtained	
6. B. N.	48	♀	Since July, 1940, angina pectoris of effort. Since January, 1941, walking only one-half block caused anginal pain. No angina of rest	Electrocardiogram taken Jan. 28, 1941, showed inversion of T_1 and T_4. These changes were progressive. Sedimentation rate (Westergren) on Jan. 21, 1941, was 21 mm.	
7. M. G. L.	56	♂	Following "flu" in August, 1938, angina pectoris of effort developed. There was never pain at rest	Electrocardiogram taken five months after the "flu" showed the signs of anterior wall infarction	
8. S. S.	62	♀	Since June, 1941, severe angina of effort. Walking one-half block caused anginal pain. Never pain during rest	Sedimentation rate (Westergren) in August, 1941, was 74 mm. Electrocardiogram (July 29, 1941) showed convex S-T segment and inversion of T in Lead I; also negative T in Leads II and III	Complicating diseases: Diabetes and hypertension

TABLE I—CONT'D

CASE	AGE	SEX	ANGINAL MANIFESTATIONS	EVIDENCE SUGGESTIVE OF ISCHEMIC MYOCARDIAL NECROSIS	NECROPSY OBSERVATIONS	REMARKS
9. M. A.	30	♀	Since August, 1941, severe angina pectoris of effort. Walking one or two blocks caused anginal pain. Never pain during rest	Leucocyte count (Nov. 13, 1941) was 12,400. Electrocardiogram (Sept. 13, 1941) showed deep Q_2 and Q_3 and inversion of T_2. The same changes in subsequent tracings		Complicating disease: Mitral regurgitation. Mother died from hypertension at the age of 36 years
10. H. J.	52	♂	Since early 1941 angina pectoris of effort. Two weeks after gastrectomy (on Nov. 4, 1941), anginal attacks occurred repeatedly during rest, each lasting about ten minutes	Temperature rose to 101.4° F. a day after the onset of anginal attacks of rest. The sedimentation rate (Westergren) increased to 37 mm. The heart sounds were distant. Progressive electrocardiographic changes suggested anterior wall infarction		Complicating condition: Hypertension
11. W. L.	48	♂	Since April, 1940, substernal pain on walking. Two brief anginal attacks, lasting fifteen minutes, occurred in the middle of June, 1940, during night	Electrocardiogram (Aug. 2, 1940) showed a convex S-T and inverted T in Lead I, and sharp inversion of T_4		
12. J. F.	68	♂	Since the beginning of 1942 tightness of the chest on walking 3 or 4 blocks. In the second week of June, 1942, walking only one block caused severe pain in the chest. Anginal attacks came also during rest, lasting up to fifteen minutes. The patient felt "worn out"	Leucocyte count (June 16, 1942) was 12,000. The electrocardiogram taken on the same day showed isoelectric T_1, absence of R_3, sharp inversion of T_2, and deep Q waves in Leads II and III		

13. H. G.	63	♂	Never angina pectoris of effort. Ten days after an abdominal operation (on May 7, 1942), attacks of substernal pain developed during rest, relieved by nitroglycerin. The attacks were brief due to the effect of nitroglycerin, and came about twice daily for two weeks	Temperature rose to 100° F. on the first day of the anginal attacks. Three days later the sedimentation rate (Westergren) was 34 mm. An electrocardiogram on May 23, 1942, showed flattening of T₁ and flattening and late inversion of T₄. These changes subsided within two weeks	Complicating condition: Hypertension with marked hypertrophy of the left ventricle
14. S. M.	62	♀	Never angina of effort. Very brief attacks of precordial pain developed in the middle of August, 1941, lasting a few seconds to a few minutes. These attacks occurred repeatedly during a period of six weeks, while the patient was at rest	Temperature rose to 100.2° F. on the first two days following admission (Sept. 26 and 27, 1941). Sedimentation rate (Westergren) on Sept. 29, 1941, was 23 mm. Leucocyte count, on Sept. 27, 1941, was 10,600. Four electrocardiograms, taken between Sept. 29 and Oct. 20, 1941, showed progressive changes resulting in inversion of T₁ and T₄	
15. L. K.	55	♂	Sudden onset of angina pectoris in May, 1942, when patient lifted a load; the pain lasted only a few minutes. In the following week three short anginal attacks during meals or excitement, none lasting more than a few minutes	Electrocardiogram (May 14, 1942) showed elevation of S-T in Lead III and depression of S-T in Lead I; also marked depression of S-T and flattening of T in Lead IV. In the following weeks, T₄ became inverted and a Q wave developed in Lead IV	
16. L. R. G.	42	♂	In September, 1940, a nocturnal attack of severe substernal pain, lasting 15 minutes. A similar attack on the next day, while driving a car; this attack lasted 10 minutes. Then severe weakness developed. Thereafter angina of effort and sometimes short attacks during night. There was never an attack lasting more than 15 minutes	An electrocardiogram taken two years after the onset of angina pectoris showed nearly isoelectric T₁ and upright T₃	

minutes. In Case 16, angina pectoris started with two brief attacks during rest. The serious meaning of these symptoms was not recognized, and the necessary rest in bed was neglected. Thereupon, marked angina of effort developed, and the patient was unable to walk one block without experiencing pain. This is a frequent event after myocardial infarction. It is remarkable that anginal attacks of rest associated with evidence of myocardial infarction (in Case 13) were promptly abolished by nitroglycerin.

One patient in Group I (Case 1) died after new and severe anginal attacks had followed the development of angina of effort. Another patient in Group I (Case 4) died suddenly, five months after the abrupt onset of angina of effort. There was no fatality in Group II.

<div align="center">COMMENT</div>

Our observations prove that angina of effort or brief attacks of angina of rest may be significant symptoms of ischemic myocardial necrosis. The practical importance of this fact with regard to management is obvious. Although the serious meaning of such atypical anginal attacks has been repeatedly mentioned in the literature, it has not been generally recognized.

Obrastzow and Straschesko[3] reported the case of a 57-year-old man who had myocardial infarction (proved by autopsy) which was clinically indicated by brief attacks of angina of rest, none of which lasted more than ten minutes. Herrick[4] has stated that ischemic myocardial necrosis of slight extent is clinically often indicated by mild anginal pain of rest. The difficulty of differentiating "angina pectoris" from minor forms of "coronary occlusion" has been stressed by Smith.[16] This author advised that "coronary occlusion" be considered whenever attacks of angina grow more severe than usual or come on at rest. Boas[17] has commented on patients who are ordinarily regarded as having common angina pectoris, but, on close questioning, admit that their complaints started with an anginal attack of particular severity, lasting not more than fifteen minutes. Such patients, in Boas' opinion, have, at the outset, suffered structural damage to the myocardium. Pardee[18] has discussed patients with electrocardiographic signs of myocardial infarction "who have never been subject to an attack which could have been due to coronary thrombosis." Our Case 7 is an example of this. After having grippe, the patient experienced angina of effort, but had never had a severe, protracted, anginal attack during rest. Electrocardiographic evidence pointed to myocardial infarction.

Bourne[19] observed a 61-year-old patient who, for four weeks, had experienced angina pectoris of effort, but not of rest; the electrocardiogram showed signs of anterior wall infarction. The author concluded that "clinically, coronary thrombosis is suggested by severe angina of effort coming on suddenly and slowly diminishing from the first on-

set.'' LeRoy and Snider[20] reported on a 49-year-old patient who had complained of precordial pain on effort for one week, and then suddenly died. Autopsy revealed old calcific occlusion of the main branches of the left coronary artery and ''a slight softening of the apical region.'' Parkinson and Bedford[5] have expressed the opinion that gradual coronary occlusion, leading to scattered myocardial fibrosis, is clinically manifested by angina of effort which becomes more frequent and more easily induced. According to Blumgart and his co-workers,[21] particular care should be given to those patients ''who suddenly develop angina of effort, mild or severe'', and also to those ''who, having had angina pectoris, experience a sudden aggravation of their symptoms.'' The authors hold that increased frequency and severity of anginal attacks denote progressive coronary insufficiency. A similar view has been expressed by Master and his associates[22] who, in a study on premonitory symptoms of acute coronary occlusion, found that a sudden onset or aggravation of angina of effort often presaged the development of myocardial infarction.

Various authors have reported on ''premonitory pain in coronary occlusion.''[5, 22-28] Myocardial infarction is often heralded by prodromal pain which occurs hours, days, or weeks prior to the ''actual attack of coronary occlusion.'' The premonitory pain may be mild or severe, and it may last a few minutes or several hours. It is mostly unrelated to effort and not influenced by nitroglycerin. Occasionally, sudden onset or aggravation of angina of effort presages the development of myocardial infarction.[22, 28] It is readily seen that the description of premonitory pain fits well into the picture of anginal symptoms presented by the patients in our study. According to the authors who have reported on premonitory pain, the latter is distinguished from ''coronary occlusion'' by the lack of evidence of myocardial necrosis, such as fever, leucocytosis, rapid sedimentation rate, and significant electrocardiographic changes. However, some of this evidence was present in the cases in our report. Moreover, careful study of the cases reported by others occasionally reveals the presence of such evidence. A conspicuous number of those patients who were subjected to electrocardiographic examination during the stage of premonitory pain showed significant electrocardiographic changes. For instance, in two cases (No. 8, Fig. 2b and No. 15, Fig. 3b) reported by Feil,[23] there were electrocardiographic signs which are considered by some authors as indicative of myocardial infarction.[13-15] In a case reported by Master and his associates[22] (Fig. 4), there were electrocardiographic changes like those attributed by the same authors to myocardial infarction in the absence of acute coronary occlusion.[29] In Boyer's[28] Case 3, there was, during the stage of premonitory pain, in addition to an increased sedimentation rate, the electrocardiographic pattern of a low R_1 with a deep S_2 and S_3; there was also a flat T_1, with high voltage of T_3. These signs are suggestive of anterior wall infarction. In the

same author's Case 5 there were electrocardiographic signs "suggesting that there had been some change in the heart muscle" during the phase of premonitory pain.

Master and his co-workers[22] have stated that "premonitory pain" was invariably followed by "typical coronary occlusion." However, in some cases reported by Sampson and Eliaser,[25] such a sequence of events did not take place. In our group of cases, "prodromal pain" was only once (Case 1) followed by the typical clinical picture of myocardial infarction. Sampson and Eliaser and Master and his associates have stressed the difficulty of distinguishing premonitory pain from "actual coronary occlusion," especially in cases in which the premonitory pain was severe and protracted. Our own experience and the evidence offered in the reports of others[22, 23, 28] suggest that such a distinction is often artificial. "Premonitory pain" usually indicates progressive coronary insufficiency, and is most often associated with ischemic myocardial necrosis which may or may not be followed, after a period of days or weeks, by more extensive myocardial infarction.

Atypical anginal pain like that in the cases of our report is probably associated with myocardial necrosis of lesser extent; it is possibly due to sudden occlusion of small coronary branches,[4, 11] or to gradual narrowing of coronary arteries.[6, 21] It should be mentioned that electrocardiographic changes which are often associated with massive infarction, such as a high take-off of S-T in Lead I, absence of R_1, and low voltage of QRS in the standard leads, were lacking in our cases. Postmortem examination in cases of coronary arteriosclerosis often reveals the presence of small areas of fibrosis which had escaped clinical diagnosis. It is likely that the anginal symptoms in the cases of our report represent the clinical counterpart of these anatomic changes.

The practical implications of recognizing the serious meaning of atypical, mild anginal attacks are obvious. Although it is unlikely that complete occlusion may be obviated by rest in bed in cases of progressive coronary thrombosis, it is generally agreed that the deleterious effect of inadequate blood supply to the myocardium is reduced by diminishing the strain on the heart. This is particularly true when myocardial infarction develops in the absence of occlusion, which happens in about 30 per cent of the cases of myocardial infarction.[26] Strict rest in bed should be instituted whenever a sudden onset or aggravation of angina of effort, or the appearance of brief attacks of anginal pain during rest, points to progressive coronary insufficiency.[11, 16, 20, 21, 28] In such cases, ischemic myocardial necrosis is often present, as is suggested by the observations of this study. Sudden death is most frequent among cases of unrecognized myocardial infarction in which there are only mild symptoms.[4, 11, 17, 29] Experimental and clinical evidence suggests that death is often due to ventricular fibrillation caused by reflex vasoconstriction of the coronary arteries, which is in-

duced from the infarcted area.[20]   Therefore, the use of vasodilators, such as atropine, aminophylline, and papaverin, during the early stage of myocardial infarction has been advised as a lifesaving procedure.

A thorough history is of paramount importance in the recognition of progressive coronary insufficiency which may early result in the formation of small areas of necrosis.   One should not be satisfied with the plain diagnosis of angina of effort.   It is indispensable in every case to ascertain the present and past functional capacity of the heart, i.e., the amount of effort that produces anginal pain.   Any sudden change in the functional capacity indicates progress of the coronary disease, and this demands complete rest in bed for at least three weeks, until collateral circulation has developed to supplement the deficient blood supply.[34, 35]   Anginal attacks during the night or after meals (in the absence of any additional effort) should also be considered as warning signals.   A suspicion aroused by the history is often supported by finding that the sedimentation rate is increased.   This is occasionally a more sensitive index of myocardial necrosis, when other causes can be ruled out, than the electrocardiogram,[31] and "may presage a coronary attack by weeks and months."[32]   It is of interest that Riseman and Brown[33] have observed an increase in the sedimentation rate in more than 50 per cent of cases of angina pectoris.   They expressed the opinion "there is reason to believe that attacks of angina pectoris occasionally result in myocardial damage."   Lack of electrocardiographic changes should by no means be a reason for abandoning a diagnosis of myocardial infarction which is otherwise clinically well founded.   In view of the serious dangers involved in neglecting the warning symptoms of progressive coronary insufficiency, I would subscribe to the advice of LeRoy and Snider:[20]   "Suspicion rather than certainty should determine the psysician's conduct."

SUMMARY

This is a report of sixteen cases in which there was clinical and laboratory evidence suggestive of myocardial infarction, although characteristic, severe, and protracted anginal attacks were lacking.   In nine cases, myocardial infarction was indicated by the sudden onset or aggravation of angina of effort; in seven instances, it was clinically signalized by brief attacks of angina of rest, lasting up to twenty minutes.   Similar observations are quoted from the literature.

The seriousness of such atypical anginal manifestations is often unrecognized, and proper management of the patients is neglected.   Sudden death is frequent among this group of cases.   A painstaking history, including an accurate estimate of the functional capacity of the heart and a comparison of present and past performances, furnishes the most significant diagnostic data.   An increase in the sedimentation rate is often a more sensitive index of myocardial necrosis than are electro-

cardiographic changes. Lack of the latter should never be considered as conclusive evidence against serious myocardial involvement.

Anginal pain like that in the cases in our report has often been designated as "premonitory pain," which precedes the development of "actual myocardial infarction." Our own experience and reports in the literature prove that "premonitory pain" is not invariably followed by typical anginal attacks signifying myocardial infarction. Moreover, "premonitory pain" is often by itself associated with evidence of myocardial necrosis. Hence, it appears that the distinction between "premonitory pain" and "actual myocardial infarction" is inappropriate. A sudden onset or aggravation of angina of effort, or brief attacks of angina of rest indicates progressive coronary insufficiency, and is in the majority of cases, associated with ischemic myocardial necrosis.

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CONTINUOUS RECORDING ELECTROCARDIOGRAPHY

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INTRODUCTION

D URING the past few decades electrocardiographic apparatus has
developed very rapidly. From delicate, cumbersome instruments
the machines have become sturdy and compact, so that, whether they
use the original string technique or the amplifying tube, they are now
readily portable. None of the mechanical refinements, however, has
made it possible to record an electrocardiogram continuously over a
long period of time. There are important occasions when such data
are desirable. With this in mind, a continuous recording electrocardio-
graph has been devised.

The nearest approach to what may be considered continuous record-
ing is the Asher-Hoecker apparatus,[1] which produces a fluorescent
electrocardiographic image that fades out in less than one minute.
The duration of a visible electrocardiographic complex or of several
succeeding cardiac cycles, therefore, is limited by the persistence of
fluorescence. The Asher-Hoecker "Cardioscope" is a useful instrument
in many ways, but is inadequate for detailed electrocardiographic
analysis. The gradual or instantaneous transitions, which require pre-
cise analysis, are limited to less than a minute of observation, and
thereafter the image is completely lost. Furthermore, it is inconveni-
ent, if not physically impossible, to view fluorescent electrocardio-
grams constantly for prolonged periods of time and to describe in
detail all that has happened. This may be partially circumvented by
simultaneously taking short records with the ordinary electrocardio-
graph, but gradual transitions are permanently lost, and the constant
presence of a competent observer is required.

DESCRIPTION OF APPARATUS*

Some of the continuous electrocardiographic registrations may last
as long as twenty-four hours. The ordinary instrument is incapable
of continuously registering cardiac action potentials over such a long
period of time because of electrical and camera limitations. We will
first consider the camera mechanism and the problems involved.

Camera.—At the customary electrocardiographic speed of 25 mm. per
second, the film consumption is 300 feet per hour, or 7,200 feet in twenty-

four hours.   As far as we know, the largest roll of film commercially available is approximately 175 feet long, and not all of that roll can be absorbed by the exposed record container.   Even if it is assumed that a 175-foot roll of film could be run through the camera mechanism continuously, it would be sufficient for only a 35-minute record.   If a camera were devised to accommodate the huge 7,200-foot roll of film required for twenty-four hours of operation, many obstacles of a serious nature would still be present.   For example, the physical dimensions of the
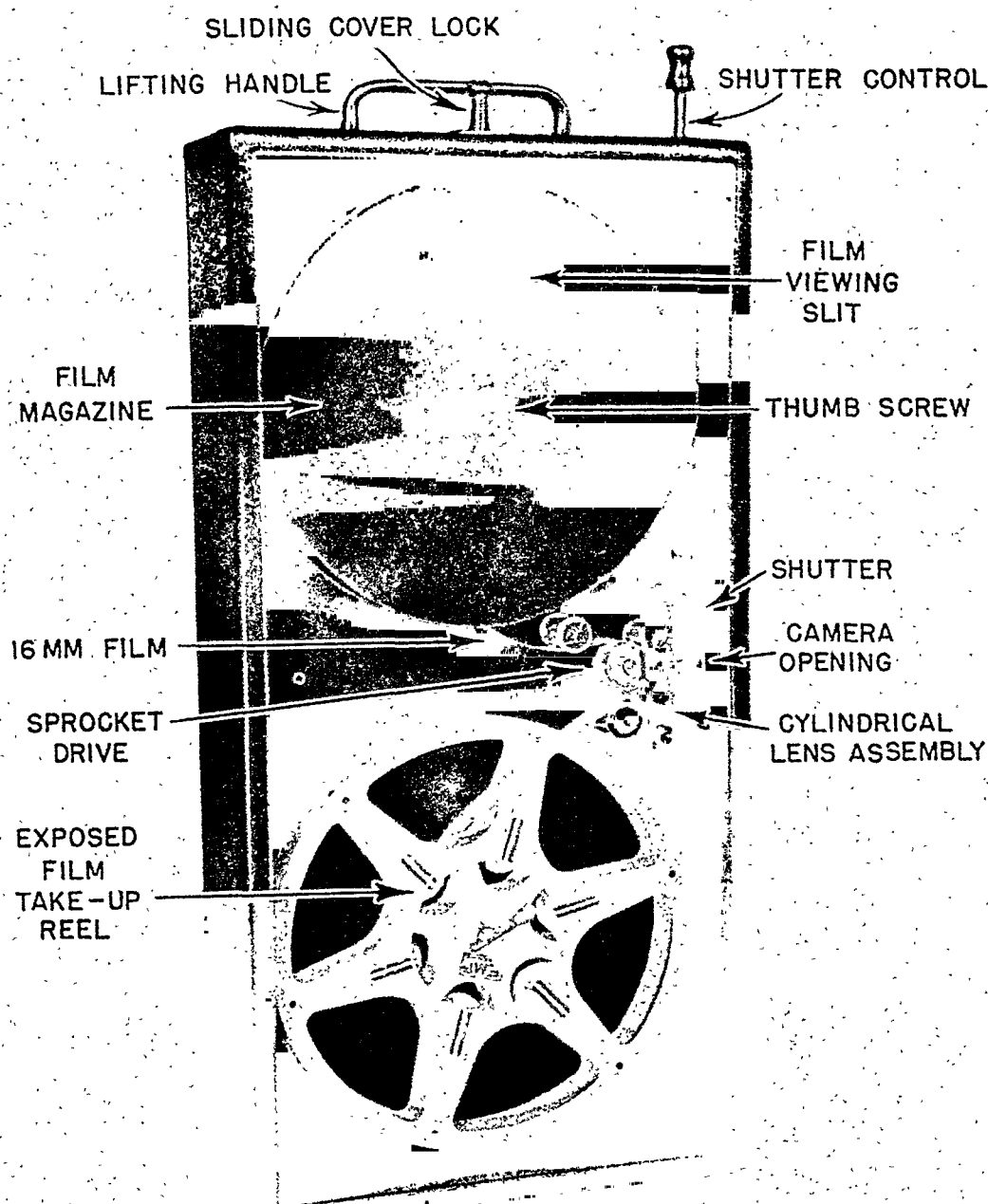
Fig. 1.—Photograph of the camera mechanism with the light-proof sliding cover removed.

camera would make it unwieldy.   Proper lengths of film or bromide paper would not be commercially available except, possibly, on special order.   The film cost would be high, and the developing, processing, and handling problems would be difficult.

It was decided that a solution to the problem would be to devise an electrocardiographic apparatus capable of registering the action potentials in miniature on 16 mm. moving picture film. The miniature record could then be studied with the aid of a photographic enlarger or projector, which would reproduce the electrocardiogram in normal dimensions. Four-hundred-foot rolls of 16 mm. film are standard and commercially available. If a twentyfold over-all reduction is made in the size of the recorded electrocardiogram and in film speed, 400 feet of film are sufficient for 26.7 hours of continous operation. The effective or workable width of the 16 mm. film is 10 mm., for the sprocket holes consume 6 mm. Therefore, at a twentyfold reduction in the deflection amplitudes of the complexes, the 10 mm. working width is actually the equivalent of 20 cm. film with normal electrocardiographic deflection amplitude (one centimeter per millivolt).
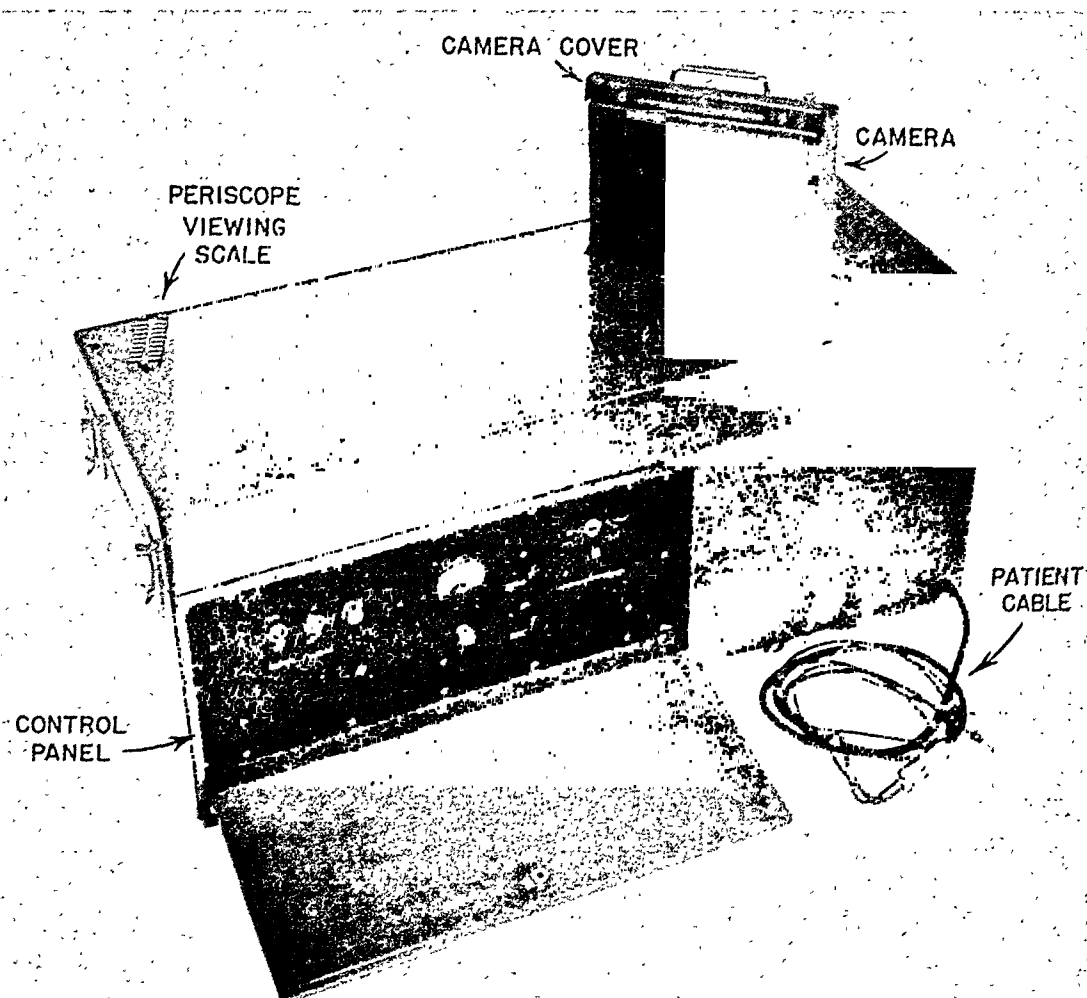
Fig. 2.—The continuous recording electrocardiograph.

Fig. 1 is a photograph of the camera mechanism, with the light-proof sliding cover removed. The roll of 16 mm. film is placed in the magazine and threaded through the guide rollers and sprocket drive to the exposed film take-up reel. The sprocket is connected to a synchronous motor by means of a gear train. When the camera is lowered into the electro-

cardiographic mechanism (Fig. 2), the gear coupled to the sprocket engages another gear which is directly coupled to the synchronous motor. The exposed film take-up reel is connected to the sprocket by means of a pulley system and spring belt. A synchronous, alternating current motor drive is used because its speed is constant under all conditions of operation. The timing of the electrocardiogram is based upon the speed at which this motor rotates. The rotation of the motor causes the sprocket to rotate in a clockwise direction. This action pulls the film from the magazine to the exposed take-up reel past the camera opening and cylindrical lens assembly. The spring belt drive connecting the sprocket and take-up reel is so designed as to keep the film under tension. As a result, the exposed film winds up into a snug roll on the reel. The shutter control is merely a device to close the camera opening when carrying the camera to and from the darkroom.
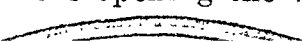
The Optical System.—Fig. 3 is a schematic sketch of the optical system and the other major components of the continuous recording electrocardiograph. The optical system is composed of two independent galvanometric channels; one is used for recording, and the other for viewing and standardization. A viewing channel must be used in which the deflections are exactly twenty times as large as the deflections of the recording beam, for it is impossible to judge and calibrate the instrument when 1 mv. deflects the recording beam only ½ mm. The optics of the recording channel are of an unorthodox design; this is necessitated by the unusual and exacting requirements of miniature electrocardiographic photography. The record must be extremely sharp and well defined, for the minutest flaw, when magnified twenty fold for visualization, may be sufficient to mar completely the legibility of the electrocardiogram. The cylindric or camera lens arrangement must be capable of focusing the recording beam down to a slit of light 0.0005 inch in thickness. Furthermore, this adjustment must remain fixed for the life of the instrument.

The schematic sketch (Fig. 3) indicates the manner in which the recording beam impinges upon the film. The recording condenser lens picks up a portion of the light which radiates from the incandescent lamp. The positioning and focal length of the condenser lens are such that it throws a minute image of the lamp filament through the recording optical slit to a point slightly behind the concave recording galvanometer mirror (the theoretical location of the focused image if the mirror were removed). In turn, the concave mirror reflects the beam of light and diverges it so that an image of the recording optical slit falls upon the front surface of the cylindric lens assembly. The latter squeezes the beam down to a slit of light 0.0005 inch, or less, in height; the width of the beam remains unchanged, and is dependent upon the degree of opening of the recording optical slit.

When a cardiac action potential is applied to the moving coil (d'Arsonval) galvanometer after passing through the electrocardiographic amplifier, the galvanometer coil supporting the concave mirror deflects that amount which is directly proportional to the intensity of the action potential. The motion of the galvanometer causes the 0.0005 inch slit of light to move horizontally across the film. The combination of the downward motion of the film and the transverse movement of the slit of light produces the miniature electrocardiogram.

The width of the isoelectric line is proportional to the opening of the recording slit; the greater the opening the wider the line. If the

galvanometer is stimulated by a slowly changing phenomenon, such as a P or T wave, the 0.0005 inch slit deviates from the isoelectric level at a slow rate, and the registering beam is slightly narrower than during the isoelectric phase (Fig. 4). The more rapid the deviation from the isoelectric level, the narrower the line becomes. Therefore, a QRS complex registers as a narrower line than a P or T wave. An infinitely fast deviation, such as would occur upon standardization during the transition interval, with an infinitely fast galvanometer, would produce a registration thickness equal to that of the slit of light.
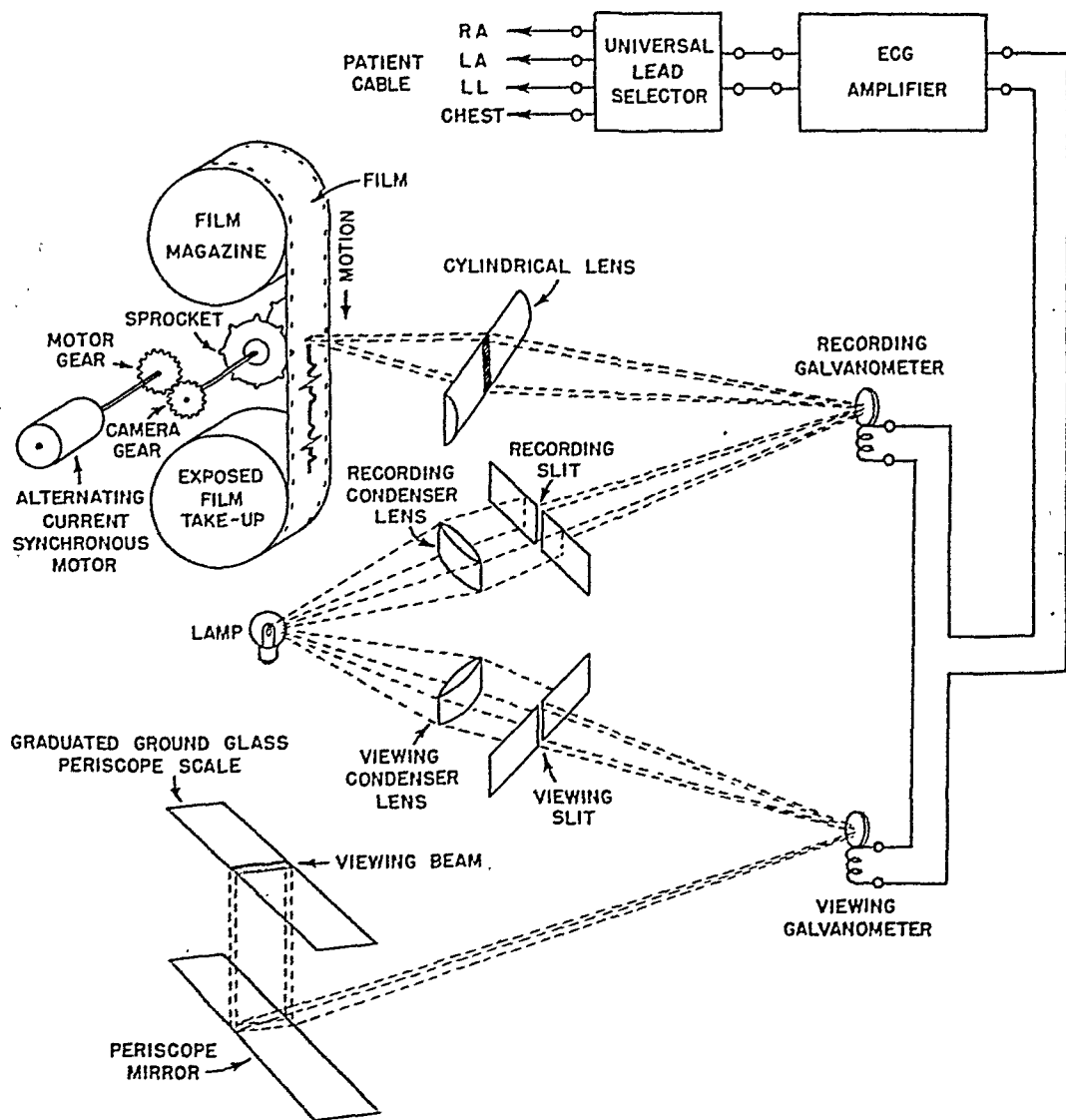
Fig. 3.—Schematic sketch of the optical system and other major components of the continuous recording electrocardiograph.

It was previously mentioned that, in miniature electrocardiography, it is essential to focus the recording beam down to a sliver of light 0.0005 inch, or less, in thickness in order to obtain good QRS definition. To illustrate, consider a condition in which a rather short QRS complex of 0.06 second is registered by a slit of light more than 0.0005 inch in thickness. At normal film speed (approximately one

inch per second), the base of the 0.06 second QRS complex is equal to 0.06 inch. In a miniature electrocardiogram, in which the over-all
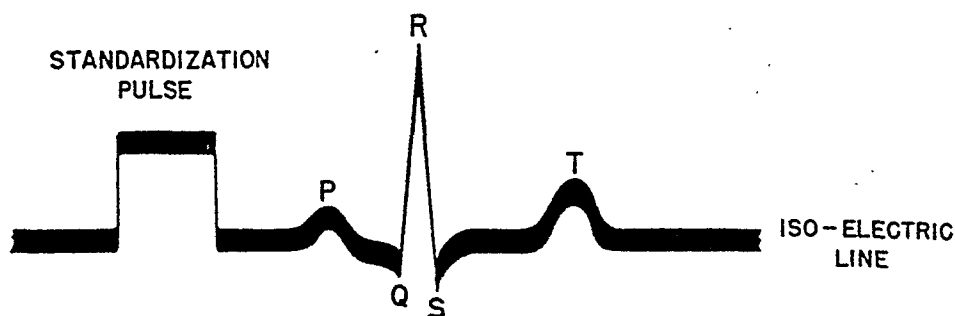
Fig. 4.—Sketch to illustrate variation in the recorded thickness of electrocardiographic complexes as a function of deflection speed.
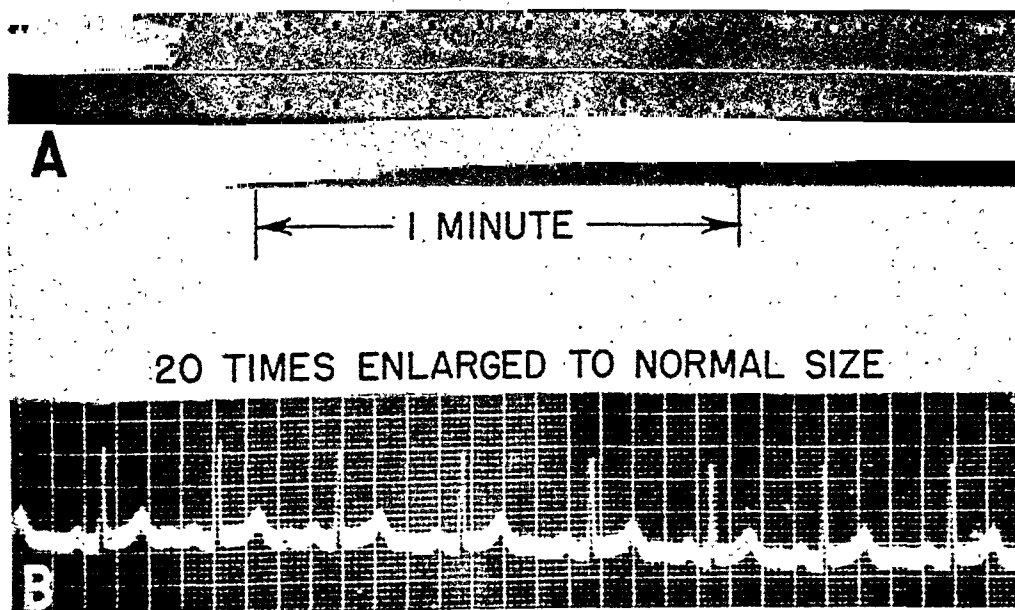
Fig. 5.—A comparison of an actual tracing and the normal electrocardiogram which was obtained by enlarging the miniature record.

dimensions of the complexes are one-twentieth normal in size, the QRS base is equal to 0.003 inch. The cylindric lens of a good commercial electrocardiograph will focus the light down to approximately 0.004 inch instead of 0.0005 inch. If a summation is made of the Q-R and R-S segments registered by a 0.004 inch sliver of light, and we take into consideration that the duration of a QRS complex is not sufficiently short to allow for the thinning out of the lines to even 0.004 inch, the Q-R and R-S segments must exceed 0.008 inch. Such registration lines are but a fraction of the actual duration of the QRS wave at a film speed of 25 mm. per second, but in miniature electrocardiography the base of the QRS complex is only 0.003 inch for a 0.06 second interval. Therefore, if a sliver of light 0.004 inch in thickness were used for recording the miniature graph, the thickness of the Q-R or R-S complex would be more than the actual QRS duration, and a blotch would result instead of a well-defined QRS complex. We have found that a 0.0005 inch beam of light produces well-defined electrocardiograms on

all human beings. The finer the focus, however, the better the photographic definition.

Fig. 5*B* is a twentyfold enlargement of the miniature electrocardiogram shown in Fig. 5*A*, which was made with a focal precision somewhat better than 0.0005 inch. In some of the subsequent figures a slight degree of "fuzziness" may be seen in the shorter QRS complexes. The slower P and T waves are unaffected and sharp. The lack of sharpness in the short QRS complexes does not interfere with the correct interpretation.

The viewing channel optical system is orthodox in design. The ground glass viewing scale is calibrated in centimeters and the instrument is standardized by adjusting the degree of electronic amplification so that the application of 1 mv. to the amplifier input circuit deflects the viewing beam 1 cm. The recording and viewing galvanometers are electrically interconnected in series to the amplifier output. The recording galvanometer sensitivity is adjusted so that it deflects exactly 0.05 cm. when the viewing galvanometer beam deflects exactly 1 cm. This galvanometric ratio is always a constant.

Electrocardiographic Considerations.—The continuous recording electrocardiographic channel must satisfy all of the following operational conditions:

1. The over-all sensitivity of the apparatus must not vary during an electrocardiographic run. Even slight variations in the sensitivity calibration cannot be tolerated during the longest possible recording period of 26.7 hours.

2. Patient resistance, which is a variable over long periods of time, must not affect the operation and sensitivity of the electrocardiograph.

3. Skin potentials must be automatically compensated, or the recording beam may drift beyond the recording limits of the camera.

4. The isoelectric level must not be susceptible to any appreciable drift for the duration of the record.

5. The apparatus must be free of internal alternating current interference, and be capable of automatically eliminating induction effects from external wiring, diathermy machines, roentgen-ray equipment, etc.

6. The instrument must be capable of operating from the house lighting system. Batteries are not practical for continuous operation.

7. The over-all electrocardiographic requirements must satisfy all the accepted standards.

8. The electrocardiograph must be capable of functioning for the duration of the test without the attention of an operator.

A galvanometer that uses the Einthoven recording technique (quartz string galvanometer) does not satisfy requirements 1, 2, 3, 4, and 8. The usual type of electrocardiograph amplifier and mirror galvanometer combination does not satisfy requirements 1, 4, 6, and 8. A specially designed amplifier and mirror or d'Arsonval galvanometric system had to be devised to satisfy all of the eight conditions fundamental to continuous electrocardiography. The characteristics of an Einthoven string galvanometer are not sufficiently flexible for such modifications.

The amplifier is of the resistance-capacity coupled variety.[2-4] The time constant of the amplifier is approximately 2.5 seconds. For more than 0.2 second the amplifier does not exhibit any decay, and thereafter the decay is gradual and a function of the time constant.[4-6] The 0.2 second,

during which there is no decay, is longer than the duration of any known human electrocardiographic complex. The galvanometric speed is approximately 0.01 second.

It was a difficult problem to satisfy the listed requirements and utilize commercial power lines as a source of energy. The average 110-volt power line may vary between 105 and 120 volts during a twenty-four-hour period, and, in addition, instantaneous variations to the extent of several volts are constantly occurring. These fluctuations must be regulated before application to the amplifier system, or they would register graphically in superposition upon the electrocardiogram. Since these fluctuations are several thousand times as large as cardiac action potentials, they would completely mar the record and drive the recording beam beyond the bounds of the camera. Likewise, the sensitivity of the amplifier would vary with the slow line voltage variations. These voltage changes were regulated to a point at which maximum fluctuations, whether instantaneous or gradual, produced insignificant deviations of the isoelectric line and created zero changes in the amplifier sensitivity. This was accomplished by electronic regulation, the only known system capable of responding instantaneously to fast and gradual line voltage variations, and requirements 1, 4, and 6 were adequately met.

The resistance-capacity type of electronic amplification satisfied requirements 2 and 3.[5, 6] Requirement 5 was met by an automatic balancing method which eliminates only the electrical disturbances external to the patient. Requirement 7 was satisfied by designing an amplifier with a 2.5 second time constant, a 0.2 second straight line characteristic, and a galvanometric speed of 0.01 second. A lead selector switch was devised which could select, in addition to the conventional leads, CR, CL, CF, and the Wilson indifferent lead. A synchronous motor was used for timing.

The Enlarger.—To study the miniature electrocardiograms and to make photographic enlargements of sections of a continuous record, the instrument shown in Fig. 6 was devised. It consists of a good quality enlarging head, with a built-in 16 mm. film carrier and guide. The film which is mounted on a rewind reel is threaded through the film carrier and guide and then attached to the second rewind reel. The film may be run to and fro through the enlarging head, depending upon which rewind is operated. Exactly twentyfold optical enlargements must be made to obtain electrocardiograms with standard dimensions. To do this with an ordinary enlarging lens, the distance between lens and viewing screen or sensitized paper must be more than is customarily used in photographic work. Furthermore, the rewind reels and viewing screen cannot be separated by too great a distance, for the observer must operate the reels and view the graph simultaneously. A reasonable distance between the enlarged image and the observer's eyes was found to be approximately 14 inches. These qualifications were met by a system of mirrors. After the light leaves the enlarging lens (Fig. 6) it is directed to mirror *A*, which reflects it to mirror *B*, which, in turn, throws the image on the viewing screen or sensitized paper. Without such a system, the height of the apparatus would be approximately three times as great, and the separation between rewind reels and viewing screen would be increased in the same ratio.

The microfilm operating technique is practically identical with that required in making ordinary photographic enlargements, or in viewing by means of a projector.

APPLICATIONS

Continuous electrocardiography has definite applications. There are certain aspects of the mechanism of the arrhythmias that can readily be studied and clarified by this method. It is often difficult to actually photograph the beginning and ending of such disturbances as paroxysmal tachycardia, fibrillation, and flutter. The very last or first complex of
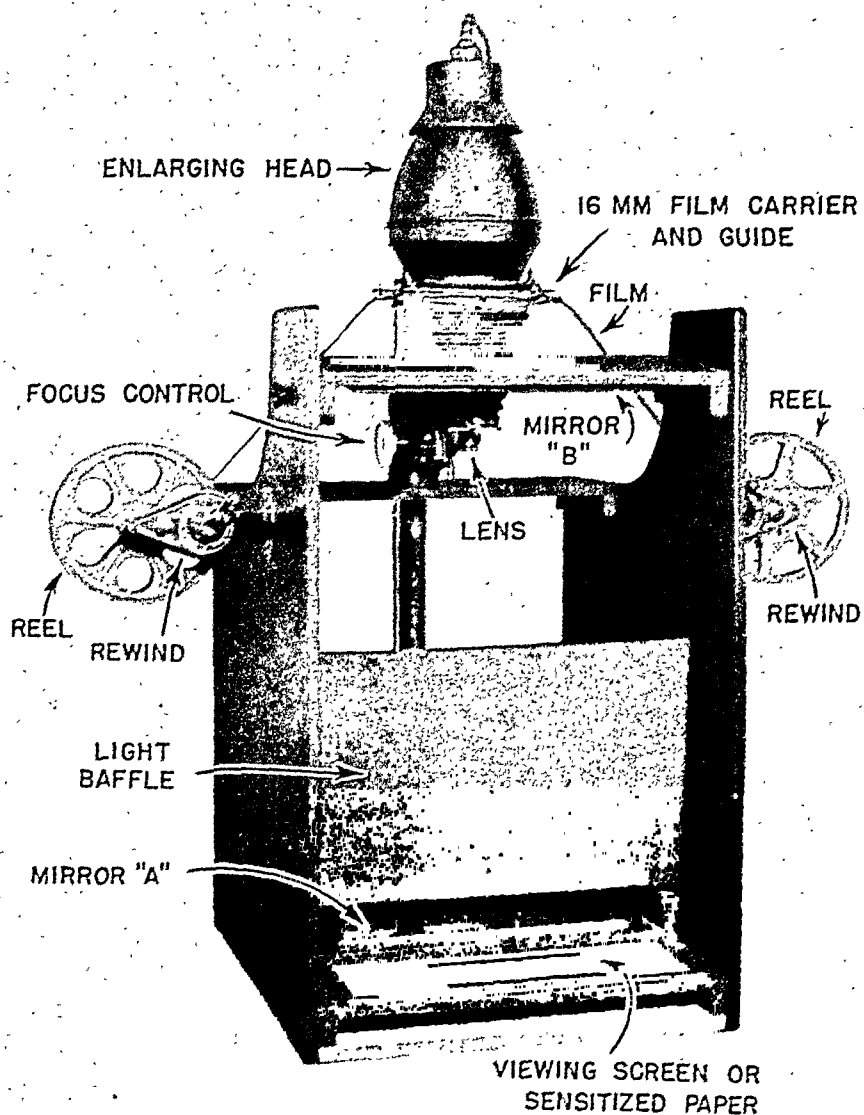
Fig. 6.—The enlarger.

such paroxysms may be the critical point in affording an explanation for the mechanism involved. Although such transitions have frequently been recorded, they generally have occurred as a result of deliberate manipulations, such as vagal stimulation, or the administration of drugs. It would be valuable to have more information concerning the spontaneous changes that occur under such circumstances, and

these are obtained only with difficulty except by continuous electro-cardiography. Even the minute and detailed effects of drugs, espe-cially intravenous therapy, on the electrocardiogram and on arrhythmias can become available for closer scrutiny.

Other observations of a more prolonged type, in which either the exact rate of the heart or the changes in the electrocardiogram itself need to be observed, could readily be investigated. The effect of labor pains, or labor itself, on both the mother's heart and the fetal rate, the effect of anesthesia in prolonged operations, the changes occurring dur-ing sleep, or during flights at high altitudes with low oxygen tension, and many other similar problems readily lend themselves to this study. Finally, it has become a matter of considerable interest to study the mechanism of death, especially in cardiac disease. Although records have been occasionally obtained which indicate that ventricular fibril-lation is the terminal event in sudden death due to coronary artery disease, more often the tracings that have been recorded when patients died were those taken after death had occurred. Furthermore, there is reason to believe that sudden death may be the result of an inhibition of contractions such as occurs in asystole accompanying Adams-Stokes disease, and not due to ventricular fibrillation. This problem is one that can be satisfactorily studied only by prolonged continuous electro-cardiography.

<center>RESULTS</center>

Eighteen continuous electrocardiographic tracings, from thirty-five minutes to ten hours in length, have been recorded. Three were ob-tained while a patent ductus was being ligated, and eight were terminal tracings taken from one to six hours before death, until there was no longer any evidence of cardiac electrical activity. Of these eight, three patients were dying of coronary thrombosis and myocardial infarc-tion, two of rheumatic valvular disease, and one each of constrictive peri-carditis, nephritis and spontaneous potassium poisoning, and pneu-monia. The remaining records were from patients with arrhythmias, and included two instances of paroxysmal ventricular tachycardia, two of complete heart block with typical Adams-Stokes seizures, and one each of auricular fibrillation, auricular flutter, and a bigeminal rhythm caused by ventricular extrasystoles.

In those cases in which a patent ductus was ligated, no specific changes were seen in the continuous electrocardiogram which could be attributed to the correction of the cardiac abnormality. Transient arrhythmias and an increase in the amplitude of the ventricular complexes were observed, but these developed prior to the ligation, and were caused either by the anesthesia, manipulation, or change in the position of the heart. A typi-cal record is illustrated in Fig. 7. The three limb leads taken just before anesthesia are shown in A, while F and G are the standard leads obtained immediately upon, and one hour after, ligation. It is seen that the nodal

beats (*B*), sinus tachycardia (*C*), nodal tachycardia (*D*), variations in T-wave amplitude, gradual development of a small S wave, and increase in QRS amplitude (*B* to *E*) occurred before the actual ligation. The transient nodal rhythm noted in this tracing was observed in the two other patients with patent ductus who were studied, but the increase in the amplitude of the ventricular complex was seen in only one of the cases.
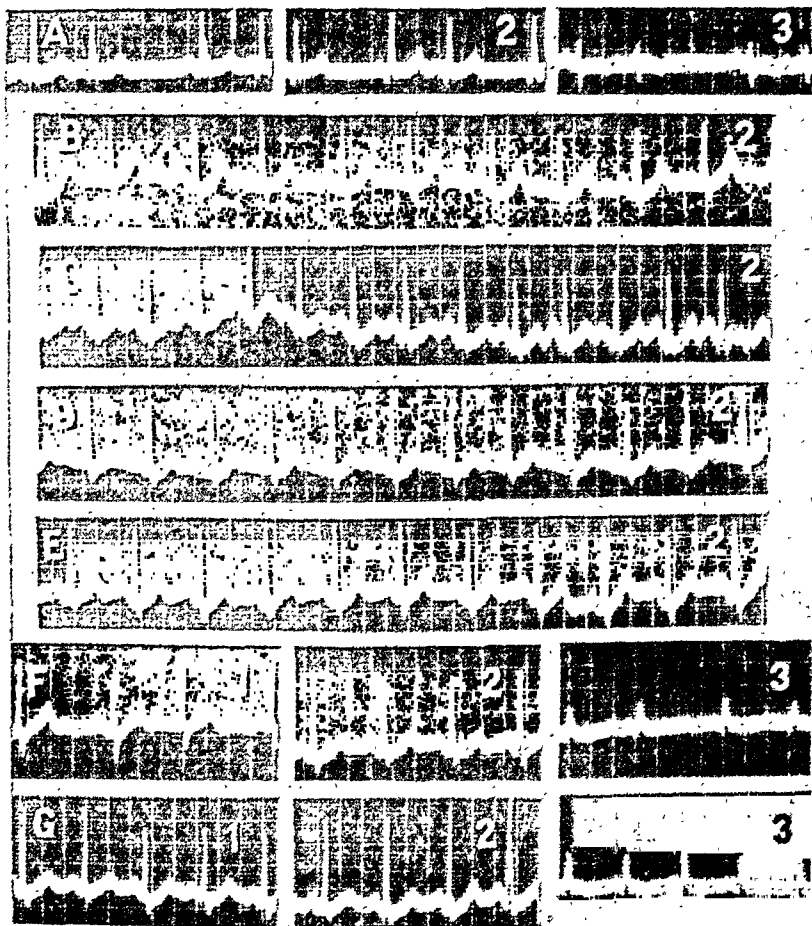
Fig. 7.—Continuous electrocardiograms taken during the ligation of a patent ductus arteriosus in a man, aged 24 years. Numbers in upper right-hand corners represent leads. Length of tracing: three hours and forty minutes. *A*, Before anesthesia; *B*, after fifteen minutes of anesthesia; *C*, thorax opened; *D*, pericardium opened; *E*, immediately before ligation of patent ductus; *F*, immediately after ligation; *G*, one hour after ligation.

It is apparent from this study that ventricular fibrillation may be the terminal rhythm when death comes gradually, for it was observed in three of eight cases. In each instance it could not be considered the actual cause of death because respirations had ceased, and, from a clinical point of view, death had already occurred. In a fourth case, ventricular fibrillation followed an intracardiac injection of adrenalin which was administered when there was no longer any evidence of cardiac activity. The sequence of events in this case (patient was a 54-year-old

man who was dying of coronary thrombosis and myocardial infarction) is seen in Fig. 8. The last spontaneous ventricular contractions (*A* and *B*) are followed by a period of asystole lasting for one minute and fifty seconds (*C*). The heart sounds were absent and there were no respirations. A needle was inserted into the heart (*D*), and a single, bizarre,
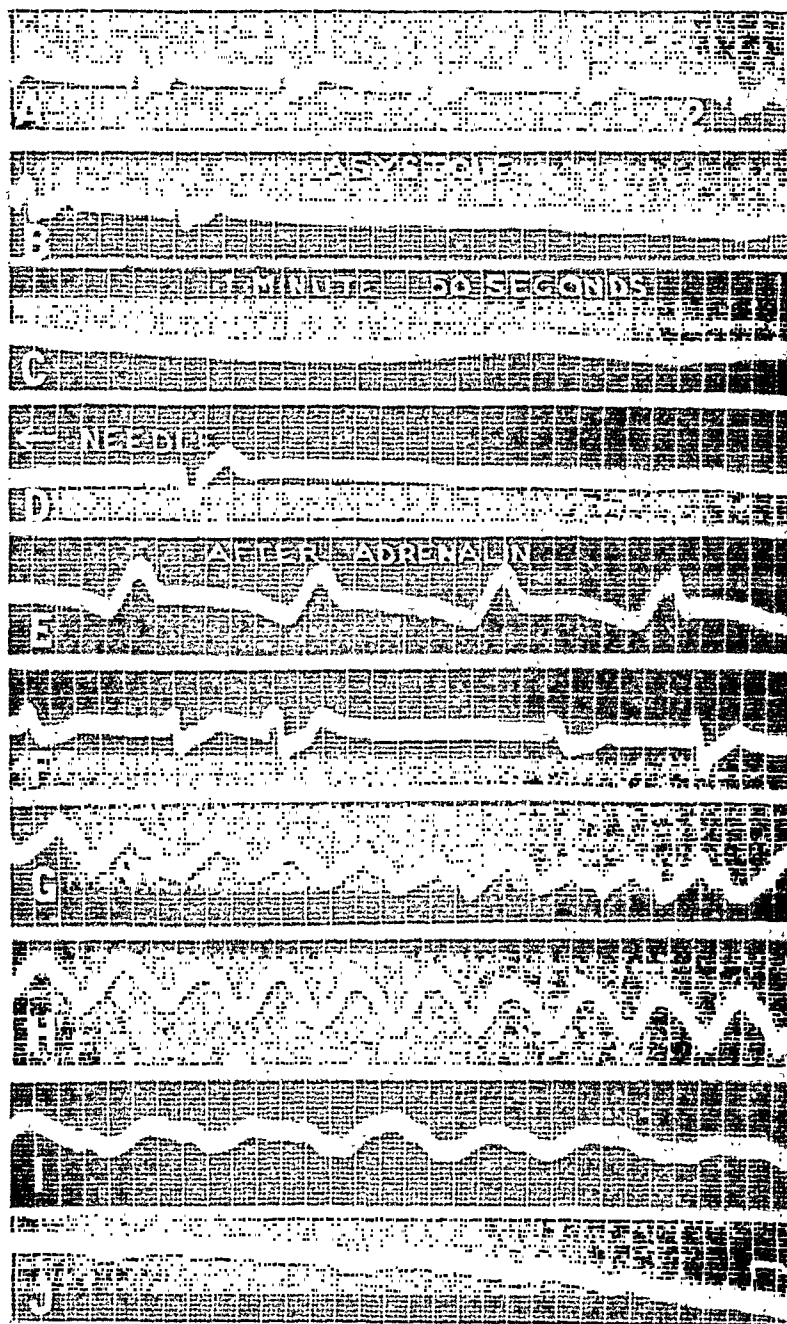
Fig. 8.—Continuous electrocardiograms (Lead II) obtained from a man, 54 years of age, dying of coronary thrombosis and myocardial infarction. Length of tracing: five hours and twenty minutes. *A*, Terminal ventricular complexes; *B*, and *C*, asystole; *D*, intracardiac needle inserted; *E*, 1 c.c. of adrenalin injected; *F*, ventricular complexes of bizarre type; *G, H*, and *I*, ventricular fibrillation; *J*, final asystole.

ventricular complex resulted. With the injection of adrenalin (*E*), ventricular impulses of a peculiar type (F) were initiated. Ventricular fibrillation then occurred (*G, H*, and *I*), followed by final asystole (*J*).

In the five patients who did not have auricular fibrillation, the sino-auricular node was the first to cease its function, but, prior to that, trantient depression and reactivation of the node were not uncommon. Fig. 9 was obtained from a 57-year-old woman who was dying of myocardial infarction. The second- and first-degree heart block (*A* and *B*), with a sinus rate of approximately 100, was followed by a sinus pause and sinus bradycardia (*C* and *D*), with a rate of only 33. This rate became more rapid again (*E*), only to slow (*F*) before all sinus activity finally ceased (*G*), fourteen minutes before death (*H*).
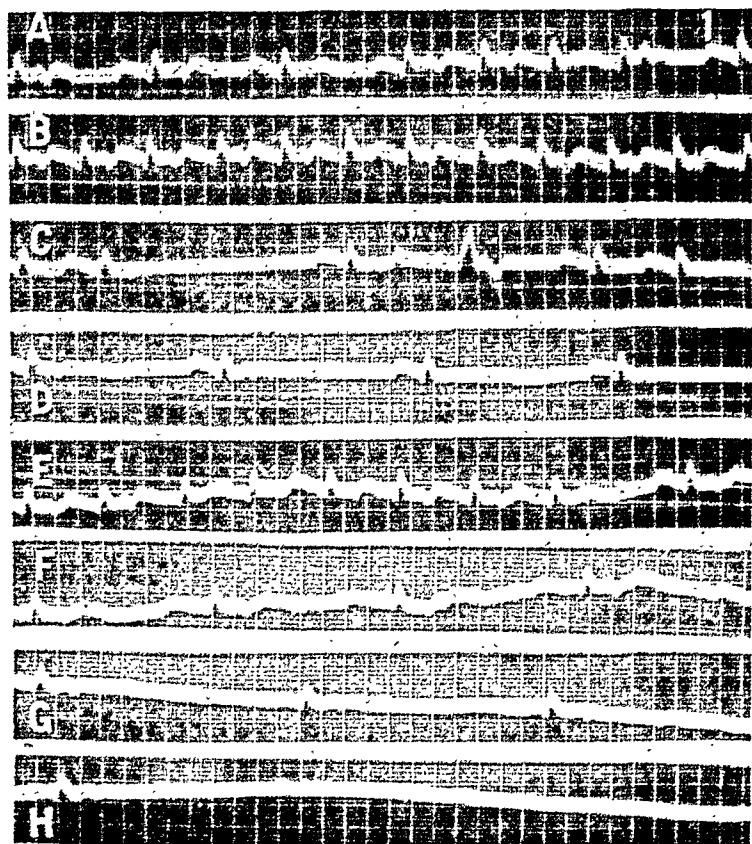
Fig. 9.—Continuous recording (Lead I) obtained from a 57-year-old woman dying of myocardial infarction. Length of tracing: three hours. *A*, Second degree heart block; *B*, first degree heart block; *C*, sinus pause and A-V block; *D*, sinus bradycardia; *E*, return of second degree heart block, and more rapid sinus rate; *F*, slowing of sinus rate, with 2:1 block; *G*, sinus activity ceases; *H*, death.

The occurrence of arrhythmias was not unusual among those patients who died gradually. At times the mechanisms were most difficult to recognize. Variations in rhythm are illustrated in Fig. 10, which was recorded in the last hours of a woman, aged 28 years, with mitral stenosis and congestive failure. A change from the gross irregularity of auricular fibrillation to a tendency to regular ventricular rhythm is seen in *A*, *B*, *C*, and *D*. This may have been due to either a nodal tachycardia, or to a peculiar regularization of the supraventricular impulses from the fibrillating auricles. The remainder of the tracing shows a slowing of

the ventricular rate (*E*), a change in the direction of the ventricular complexes (*F*), an intraventricular conduction defect (*G*), ventricular fibrillation (*H* and *I*), and death (*J*).

Another feature of the continuous electrocardiogram of the dying heart was a temporary inversion of the T waves, which was seen for periods of four to nine minutes in a patient with advanced constrictive pericarditis. In this instance, seven minutes before death the T waves became inverted and remained so until all cardiac activity had ceased.
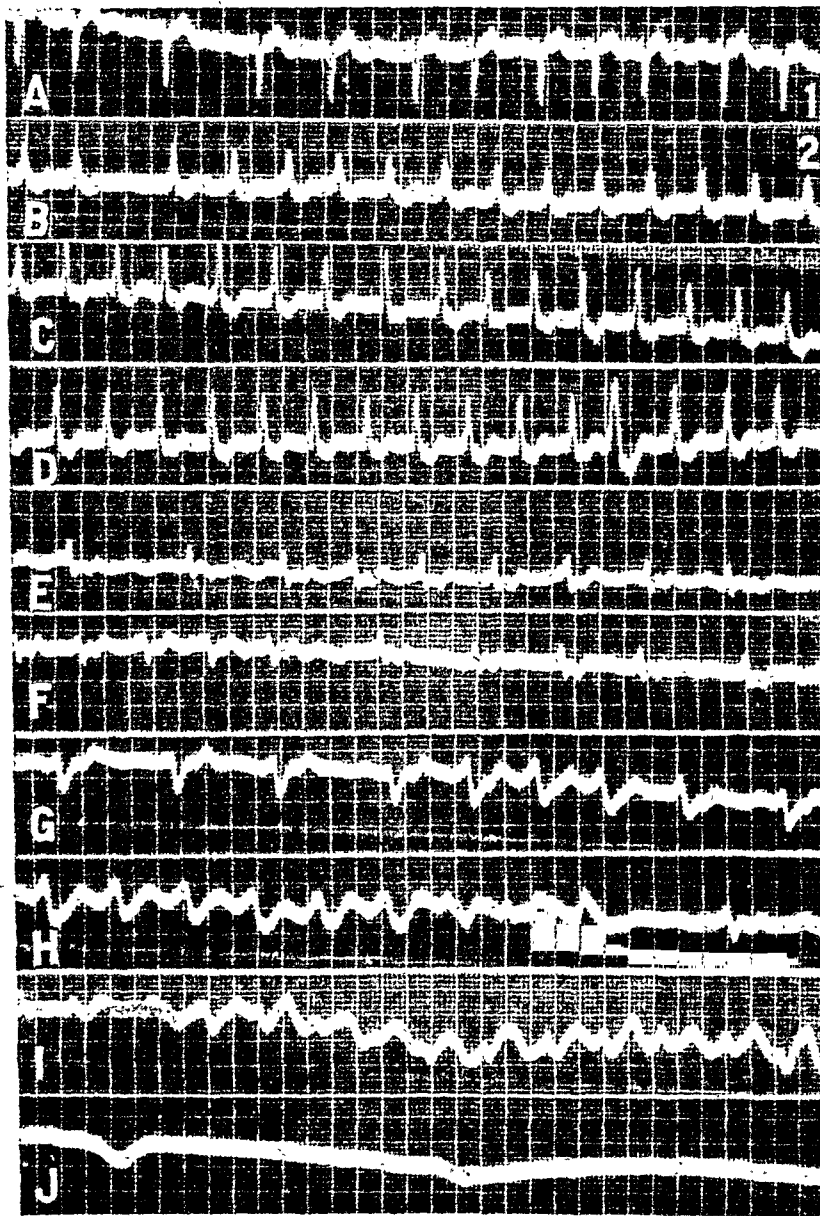
Fig. 10.—Continuous electrocardiograms taken on a 28-year-old woman dying of mitral stenosis and congestive heart failure. *A* is Lead I, and the remainder of the record is Lead II. Length of tracing: six hours. *A*, Auricular fibrillation with rapid ventricular response; *B*, *C*, and *D*, possibly nodal tachycardia; *E*, auricular fibrillation with slower ventricular response; *F*, variations in the direction of the QRS complex; *G*, intraventricular conduction defect; *H*, and *I*, ventricular fibrillation; *J*, death.

Fig. 11 is a tracing taken on a 59-year-old woman with complete heart block, right bundle branch block, and Adams-Stokes disease. Her attacks of unconsciousness lasted from several seconds to a minute. Fig. 11 *A*

represents the patient's usual electrocardiogram. In B and C, ventricular extrasystoles of different types first appear. An abnormal ventricular rhythm begins abruptly in D and continues through E and most of F, where it terminates quite suddenly. This arrhythmia most probably was ventricular flutter, and not ventricular fibrillation, for, although the patient was unconscious at the time, heart sounds were audible. This observation is quite significant, for such curves are often interpreted as
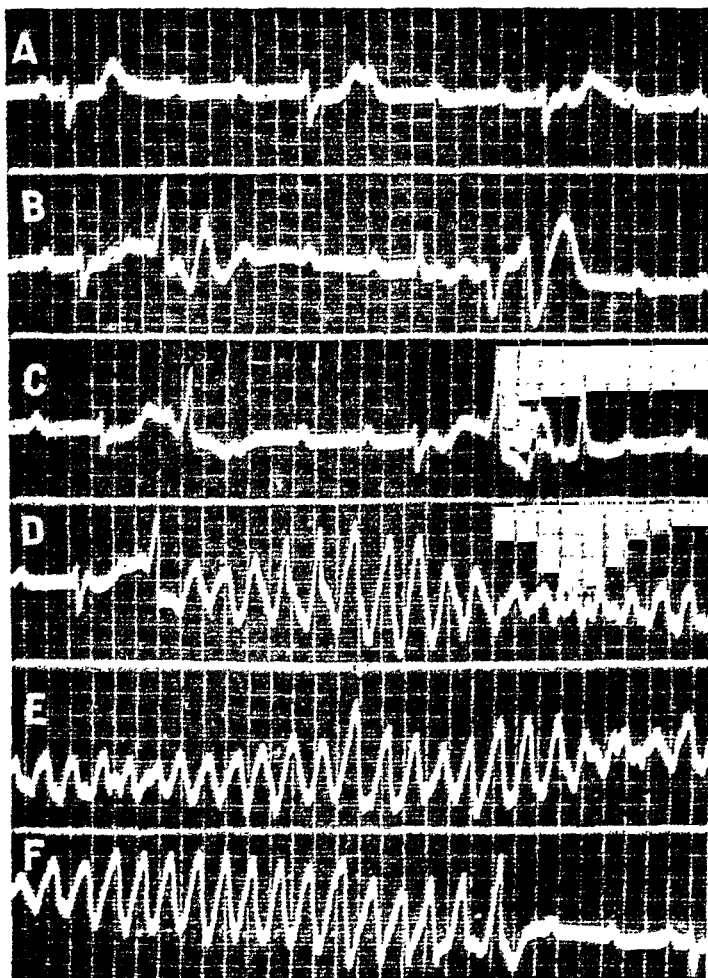
Fig. 11.—Continuous tracing (Lead I) obtained from a 59-year-old woman with complete heart block, right bundle branch block, and Adams-Stokes disease. Length of tracing: 54 minutes. A, Complete heart block. Right bundle branch block; B, and C, ventricular extrasystoles of different types; D, E, and F, ventricular flutter (heart sounds audible throughout this period); F, complete block.

ventricular fibrillation, a condition which is regarded as associated with failure of ventricular contraction. The fact that heart sounds were actually audible during the period of unconsciousness lends support to the concept that these bizarre, rapid undulations represent a mechanism that can well be called ventricular flutter. The above sequence of events recurred twenty-one times in a fifty-four-minute tracing, and the longest period of flutter lasted forty seconds.

A further interesting experience with complete heart block is pictured in Fig. 12. This woman was 65 years of age, and her usual apical rate was 32. Innumerable Adams-Stokes seizures were only partially controlled by the subcutaneous administration of adrenalin every four hours. Because of attacks of upper right quadrant pain, apparently due to a diseased gall bladder, she was operated upon, and, during the entire procedure, continuous electrocardiographic records were taken. Under ether anesthesia the ventricular rate increased to approximately 64 (A), but no further change was observed even when traction was made upon the liver and gall bladder, and when the gall bladder and common duct were artificially distended. Midway during the operation her respirations became slow and shallow, and the patient was deeply cyanotic. At the onset of this difficulty the T waves were less sharply inverted (B), and when her condition was most precarious they became quite shallow (C). Oxygen was administered and there was a prompt return of the T waves to their former configuration (D).
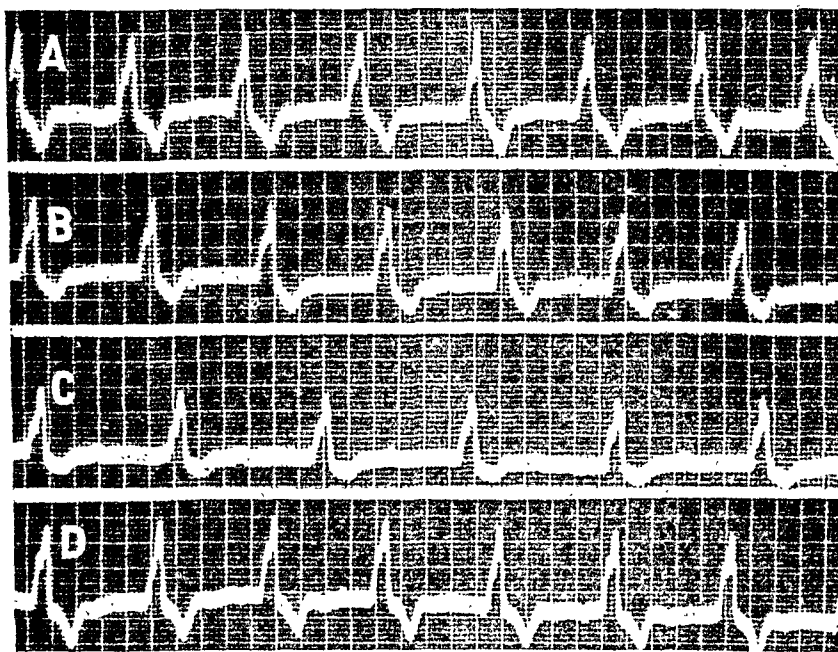
Fig. 12.—Continuous record (Lead II) on a woman 65 years of age with complete heart block, left bundle branch block, and a preoperative apical rate of 32, taken during cholecystectomy. Length of tracing: one hour and ten minutes. A, Ten minutes after administration of ether, and before first incision. Note sharply inverted T waves. Rate 64. B, and C, Respiratory distress. T waves become shallow. Rate 50. D, After oxygen. T waves again sharply inverted.

The continuous recording electrocardiograph was found to be no more difficult to operate than any ordinary portable machine. The requirements outlined under *Electrocardiographic Considerations* were fully satisfied. One tracing, heretofore not mentioned, was taken as the patient slept through the night, and no gross deviation in the recording beam was observed during the usual changes in body position. Several records were made even as the patients ate their meals. Finally, it was possible to use the apparatus in experimental work on intact large animals. Developing the film, viewing, and making enlarged reproductions

of important sections of the records were accomplished with the facilities ordinarily available in the electrocardiographic laboratory of the Peter Bent Brigham Hospital.

SUMMARY AND CONCLUSIONS

1. A continuous recording electrocardiograph was devised which is capable of taking a miniature record one-twentieth normal size upon ordinary moving picture film, and of functioning for 26.7 hours without the attention of an operator.

2. A simple enlarger was devised to view the miniature record at normal size, and to make suitable photographic reproductions.

3. The apparatus is as accurate and sturdy as the ordinary portable electrocardiograph.

4. Several interesting observations have been noted thus far. Ventricular fibrillation has been found to follow, rather than precede, death in some cases. Electrocardiographic curves generally regarded as indicative of ventricular fibrillation have been observed to occur while heart beats were audible, and therefore are better designated as ventricular flutter. Attention has also been called to other transient changes in the electrocardiogram that could be detected only by continuous tracing.

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Clinical Report

A RARE CASE OF CONGENITAL HEART DISEASE, WITH INTER-VENTRICULAR SEPTAL DEFECT, ATRETIC PULMONARY ARTERY, DEXTROPOSITION OF THE AORTA, BICUSPID RIGHT ATRIOVENTRICULAR VALVE AND SUPERIMPOSED SUBACUTE VEGE-TATIVE ENDOCARDITIS

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CASES of complete atresia of the pulmonary artery, although rare, have been reported previously.[1-4] In one case the patient lived to be 33 years of age.[1] However, we have been unable to find any cases of bicuspid right atrioventricular valve in the literature. In the case presented in this paper there were not only complete atresia of the pulmonary artery, an interventricular septal defect, and dextroposition of the aorta, but also a bicuspid atrioventricular valve on which was superimposed a subacute vegetative endocarditis. We believe this combination is unique.

CASE REPORT

L.D., an 8-year-old Italian girl, was admitted to the Pediatric Service of the Jewish Hospital in Philadelphia, Oct. 27, 1942, complaining of dyspnea, cyanosis, swelling of the abdomen, and fever of two weeks' duration.

Family History.—The family history was noncontributory. There was one sibling, who was essentially normal.

Previous Medical History.—The child was a premature baby of eight and a half months. She was cyanotic at birth, and always had had blue lips and spells of dyspnea.

When 17 months of age she was admitted to the Memorial Hospital, Philadelphia, with a diagnosis of thrush, and was discharged after nine days. No cardiac abnormalities were noted on the hospital chart at that time.

The child seemed normal, except for her cyanotic lips and occasional attacks of dyspnea, but was subject to frequent attacks of coryza and cough. Nevertheless, she was able to play almost as actively as other children of the same age.

When she was about 2½ years old, the child developed cough, fever at night, and dyspnea on walking. The cough persisted even after the fever had subsided. Her physician made a diagnosis of congenital heart disease, and sent her to the Philadelphia General Hospital, where she remained for five weeks.

The child had an acute upper respiratory infection when admitted. Dyspnea, cyanosis, especially of the lips, a swollen face, moderate pallor, pale and bluish sclera, and prominent pulsation of both carotid arteries were noted on admission.

The chest was asymmetrical because of a decided prominence and enlargement of the precordium. A systolic thrill was felt over the precordium. The apex beat was felt in the sixth intercostal space in the anterior axillary line. Cardiac dullness extended from the left anterior axillary line to a slight distance to the right of the sternum. The heart's action was rapid and the rhythm was normal. There were loud and overlapping heart murmurs which were difficult to separate into their components. A blowing systolic murmur was heard best in the mid-precordium. A diastolic murmur was heard at the apex. The aortic second sound was clear. The pulmonic second sound was obscured by duplication of the closing sound, plus other varied sounds heard over the precordium.

The lungs were negative except for occasional râles at both bases.

The abdomen was prominent, but soft and symmetrical. The liver was smooth, and extended 1 cm. below the umbilicus. The spleen was not palpable.

There was slight clubbing of the fingers.

The hemoglobin was 71 per cent; there were 4,650,000 erythrocytes and 14,000 leucocytes, of which 46 per cent were polymorphonuclear neutrophiles and 54 per cent were lymphocytes.

A radiologic examination, made three days after admission, showed general, marked enlargement of the heart; its anterior border was against the chest wall. Except for the aortic knob, the heart presented a large, globular outline. There was slight haziness in the lungs, due to decompensation. The main bronchi were not visualized.

A radiograph, taken six days later, disclosed no change in the size and contour of the heart. Most of the enlargement appeared to be of the right ventricle. In the anteroposterior view there was no displacement of the esophagus, but in the oblique view there was slight posterior displacement.

An electrocardiogram, taken four days after admission, showed that the T waves were upright in Lead I and the S-T segments depressed in Lead II. Right axis deviation was present, which, in the presence of a congenital heart condition, was regarded as suggestive of a right-sided lesion.

The child gained weight rather rapidly while in the hospital, and the upper respiratory infection cleared up. Her general condition, however, was not good. The child stood up and walked about her crib, but she was not active and her heart often seemed badly decompensated.

The diagnosis on admission was: Congenital heart disease, with patent interventricular septum (?); patent ductus arteriosus (pulmonary stenosis).

Three days after her discharge from the Philadelphia General Hospital the child was admitted to the Children's Hospital, Philadelphia, with a diagnosis of bronchopneumonia complicating congenital heart disease.

Three times during the following ten months she was readmitted to the Children's Hospital with upper respiratory infections complicating attacks of cardiac decompensation.

Two months after the last admission the child developed fever, anorexia, and cough, and was given a cough medicine. She seemed

to improve and lost her fever, but the cough became worse and dyspnea developed.

She was again admitted to the Children's Hospital, with a diagnosis of bronchitis and cardiac failure. At this time the heart was greatly enlarged, larger even than on her previous admissions. A loud, apical, blowing, systolic murmur was heard plainly through the chest posteriorly; it became fainter in the mitral region, where there was a definite, short, high-pitched, diastolic murmur. Both the liver and spleen were enlarged. Fluoroscopic examination at that time showed a markedly enlarged heart, ovoid in shape; the transverse diameter was the wider, and the left border approached the chest wall. No mediastinal shadow was noticed on the left, but on the right an actively pulsating vascular shadow was present above the heart, parallel to the spine. In the center of this vascular mass there seemed to be a shadow. There was no special prominence in the region of the pulmonic conus.

The electrocardiogram showed marked right axis deviation.

The patient improved with sulfonamide therapy, but this had to be discontinued because of leucopenia. Two weeks later she developed nasopharyngitis, but soon improved with sulfonamide treatment and was discharged.

The child then remained in fair health for a period of about four years, during which she had no fever or cyanosis, according to her mother.

Physical Examination.—Examination at the time of admission to the Jewish Hospital revealed an emaciated, cyanotic, and moderately dyspneic white female child, aged 8 years and 4 months, with marked clubbing of the fingers and cyanosis of the fingers and toes. The pharynx was injected and the tonsils were hypertrophied and infected. There was visible pulsation of the veins in the neck. The left border of the enlarged heart was in the midaxillary line. The heart beats were 140 a minute and regular. A loud, blowing, systolic murmur was heard over the entire chest and back, with maximal intensity in the third left intercostal space just to the left of the sternum. The blood pressure was 90/70 in the arms, and 120/80 in the legs. There were a few subcrepitant râles at the bases of the lungs. The abdomen was enlarged. The lower border of the liver was 4 cm. below the costal margin in the nipple line on the right. The spleen extended down into the pelvis. Both organs were smooth and not tender. There was no evidence of ascites or edema of the ankles. No petechiae were seen in the skin, nail beds, sclerae, or fundi of the eyes. There was moderate, generalized lymphadenopathy. The rectal temperature was 102° F. The respiratory rate was 30 per minute.

According to Dr. Alexander Margolies, the cardiologist to the hospital, the most likely diagnosis was the Eisenmenger complex (ventricular septal defect, dentroposition of the aorta, and right ventricular hypertrophy), although the tetralogy of Fallot (the above plus pulmonic stenosis) was considered.

Course in Hospital.—The patient's course in the hospital was irregular, but she grew progressively worse. The temperature ranged between 99° F. and 104° F., at times reaching 106° F. There were several frank chills. The radial pulse rate varied between 80 and 160 beats per minute. The dyspnea and cyanosis became worse, necessitating the use of an oxygen tent most of the time. The patient was given digitalis to the point of tolerance. Although the patient appeared

relatively comfortable at times, the signs of cardiac failure became more marked. Chills became more frequent. Despite constant oxygen therapy, digitalization, and sulfonamide therapy, the patient died Feb. 16, 1943.

Laboratory Studies.—Urinalyses showed an acid urine with a specific gravity varying between 1.020 and 1.030, traces of albumin, but no sugar or acetone. Microscopic examination of the urine showed a few leucocytes per high-power field, infrequent erythrocytes per high-power field, and, on numerous occasions, many hyaline and granular casts.
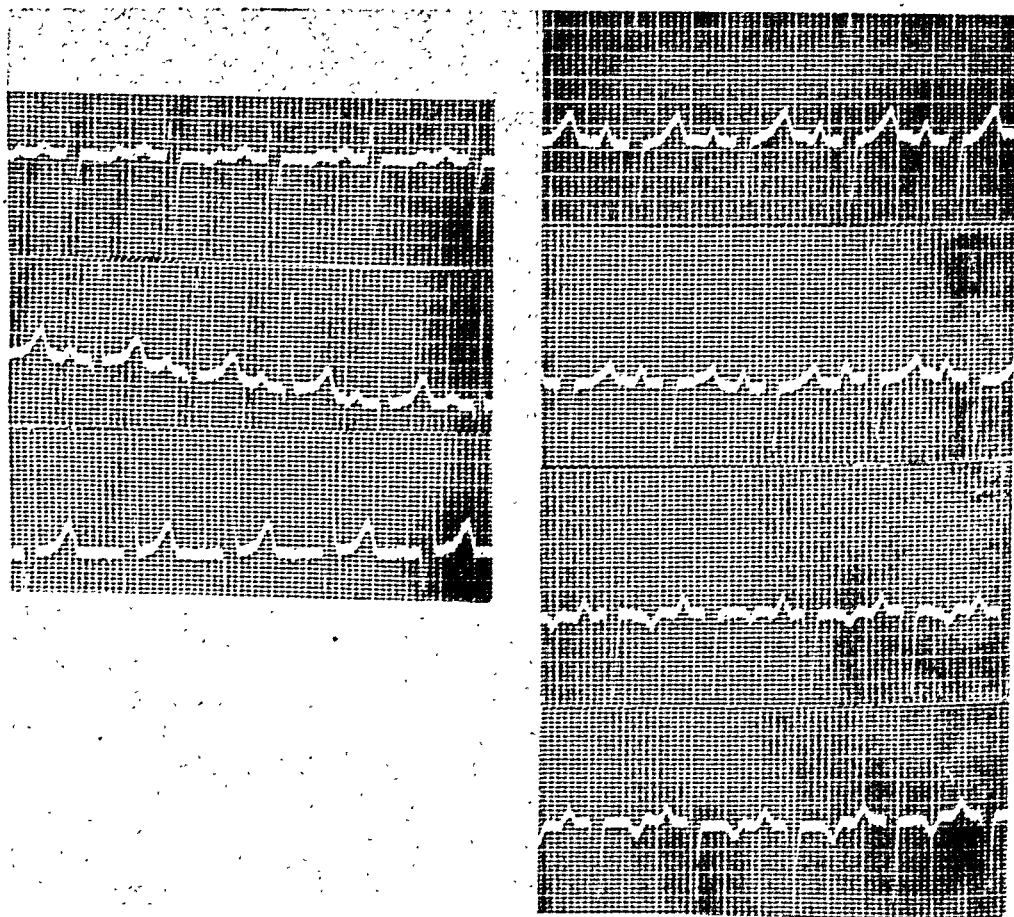
Fig. 1.

Smears and cultures of catheterized urine specimens were always negative. Although the two-hour phenolsulfonephthalein excretion test showed 25 per cent excretion in the one-hour specimen and 10 per cent excretion in the two-hour specimen, the Fishberg concentration test twice showed a concentration up to 1.030, and the blood urea on several occasions failed to exceed 15 mg. per 100 c.c. of blood. Blood examinations showed an average hemoglobin of 11.4 Gm. (83 per cent), 4,000,000 erythrocytes, and a leucocyte count which varied from 5,000 to 8,000, with a differential count of 54 per cent neutrophiles and 46 per cent lymphocytes. No abnormality of the cells was noted on smear. Blood platelet counts were normal. A bone marrow aspiration biopsy showed nothing abnormal. Of twelve blood cultures taken during peaks of fevers or chills, eleven remained sterile, and one was reported

Fig. 3.

Fig. 2.

Fig. 2.—Notice diffuse, egg-shaped enlargement of entire heart. Absence of normal shadows of the great vessels. Trachea not displaced.

Fig. 3.—Lateral view. Notice encroachment anteriorly and posteriorly of the heart on the anterior and posterior mediastinal spaces. Again the egg-shaped appearance of the silhouette.

as showing a Gram-positive diplococcus, identification of which was impossible. Blood smears for malaria parasites were negative. The stools were reported as normal. Serum agglutination tests for typhoid fever, paratyphoid fever, and the Weil-Felix reaction were negative. A heterophile antibody agglutination test was positive up to a 1:8 dilution. All blood chemical examinations were negative. The blood Wassermann reaction was negative.

An electrocardiogram revealed evidence of right axis deviation (Fig. 1). An orthodiagram disclosed an enormously enlarged heart (103 per cent above the predicted normal), a cardiothoracic ratio of 73 per cent, and a globular configuration. No prominence or pulsations were noted in the pulmonic area. Radiologic examination of the chest showed a normal diaphragm, tremendous enlargement of the heart to the left,

Fig. 4.—Abdomen, showing gross enlargement of the liver and spleen.

some enlargement to the right, and considerable enlargement both anteriorly and posteriorly, and intensification of the vascular markings in the pulmonary fields. (Figs. 2 and 3.)

A radiograph of the abdomen revealed an enlarged liver and spleen. (Fig. 4.) Roentgenograms of the long bones failed to show any evidence of lipoid storage disease, leucemia, or renal rickets.

POST-MORTEM OBSERVATIONS

The autopsy was performed by one of us (J. Z.) two hours after death. The skin was intensely cyanotic. The veins of the neck were

engorged. The abdomen was distended. The fingers were clubbed and cyanotic. There were no petechiae.

Heart.—The organ weighed 290 Gm. The muscular tone was good. The color was beefy-red. The left ventricular wall measured 10 mm. in thickness. The right ventricular wall measured 8 mm. in thickness. Both ventricular cavities were markedly dilated, especially the right. The auricular appendages contained no thrombi. The atria appeared normal. The mitral valve was normal in thickness and appearance. The right atrioventricular valve had only two cusps, a large posterior one and a smaller anterior one. On the anterior cusp there were a few vegetations covering an area of 4 mm. on the atrial surface. The vegetations were polypoid (Fig. 5). There was an interventricular septal defect in the upper anterior portion of the septum, measuring 3 cm. in diameter. The aorta communicated with both ventricular cavities and was markedly dilated. There was no pulmonary artery, or any vestige of such a structure (Fig. 6). The foramen ovale was closed. The branches of the descending thoracic aorta were markedly enlarged.
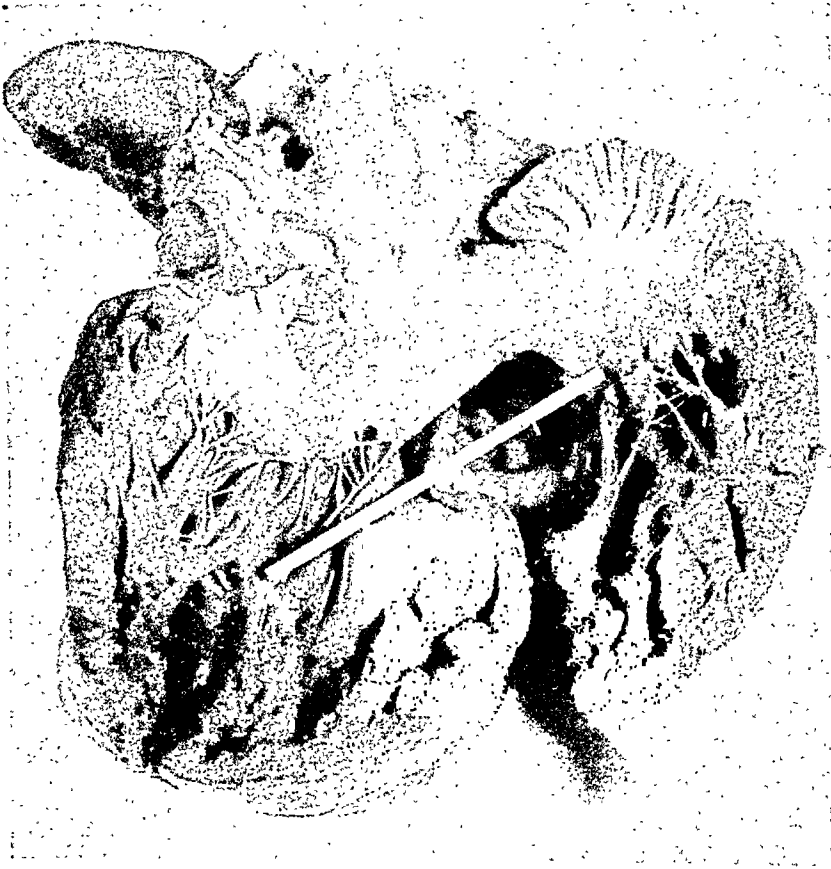
Fig. 5.—This view shows the bicuspid right atrioventricular valve. On the left is the large posterior cusp. The indicator points to the polypoid vegetations on the smaller anterior cusp.

Lungs.—The tracheobronchial tree was congested. No pulmonary artery was seen entering the hilum of the lung. The pulmonary veins, however, were traced back to the left atrium. There were numerous areas of atelectasis. No areas of infarction were seen.

Spleen.—The organ weighed 650 grams. The capsule was smooth. The organ cut with uniform and increased resistance. On cut section, the pulp was intensely congested, and the follicles were distinctly prominent and enlarged.

Kidneys.—Each weighed 160 grams. The capsules were smooth and stripped easily, leaving smooth congested surfaces. On cut section the parenchyma was intensely congested. The relationship of medulla to cortex was normal. The pelves and ureters were normal. No areas of infarction were seen.

Liver.—Weight, 1,500 grams. The surface was smooth. The organ cut with uniform resistance. On cut section there was a "nutmeg" appearance. The intervening parenchyma was pale and softer than normal.

All the other organs appeared grossly normal.

A *blood culture* taken at the time of autopsy remained sterile. A *smear and culture of the vegetation* on the heart valve failed to reveal any organisms. No anaerobic culture technique was used for any of the cultures taken during life or at autopsy.

Fig. 6.—View of the heart from above and anteriorly. The upper indicator is passing through the interventricular septal defect. The right ventricular cavity is on the left. Note the large aorta overriding both ventricular cavities. Note the absence of a pulmonary artery. The aorta is markedly enlarged.

Microscopic examination of the organs revealed the following facts:

Heart: Hypertrophy and cloudy swelling. Sections of the vegetation on the valve revealed deeply set colonies of organisms. There was a fibroblastic reaction beneath the vegetation. The organisms were gram-positive.

Lungs: Chronic passive congestion; chronic interstitial pneumonitis.

Spleen: Chronic passive congestion; reticulo-endothelial hyperplasia; marked hemosiderosis.

Kidneys: Focal glomerulonephritis; marked toxic nephrosis.

Adrenals: Hyperplasia of the medulla.
Liver: Chronic passive congestion; hepatosis; focal necrosis.
Pancreas: Chronic passive congestion.

COMMENT

The mechanics of the circulation when the pulmonary artery is atretic has been explained in previous reports as due to a compensatory enlargement of the bronchial arteries; these vessels take over the functions of the absent pulmonary vessels. It would appear, then, that the larger the bronchial arteries become, the better is the prognosis. This has been shown to be true of two patients who lived for long periods of time, and in whom the bronchial arteries were the size of pulmonary vessels.

It is not uncommon for subacute bacterial endocarditis to involve congenitally defective valves. Gelfman and Levine[5] found over 60 cases of bacterial endocarditis in 634 cases of congenital heart disease. In their review of the literature, as many as 30 per cent of congenitally defective hearts were found to be also affected by endocarditis. The reason for this is unknown, and it is not our purpose to seek an explanation here. Although there was only one positive blood culture, and it was impossible to identify or isolate the organism, the clinical course suggested subacute bacterial endocarditis. This was corroborated at autopsy, when the vegetations characteristic of the disease were found on the bicuspid right atrioventricular valve. In interventricular septal defects the endocarditis is more often found on the margins of the defect, and in one case was found on the right ventricular wall opposite the malformation.[6] The interventricular septal malformation was spared; the valve was affected.

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2. East, T., and Barnard, W. G.: Pulmonary Atresia and Hypertrophy of the Bronchial Arteries, Lancet 1: 834, 1938.
3. Bach, F.: A Case of Congenital Morbus Cordis Studied Over a Period of Twelve Years, Lancet 1: 1009, 1928.
4. Myers, B.: Case of Congenital Cyanosis, Proc. Roy. Soc. Med. 19: Clinical Section, 43, 1926.
5. Gelfman, R., and Levine, S. A.: The Incidence of Acute and Subacute Bacterial Endocarditis in Congenital Heart Disease, Am. J. M. Sc. 204: 324, 1942.
6. Eigen, L. A., and Abel, A. R.: Subacute Bacterial Endocarditis on the Right Ventricular Wall Opposite a Ventricular Septum Defect, Am. J. M. Sc. 202: 207, 1941.
7. Abbott, Maude, E.: Atlas of Congenital Heart Disease, New York, 1936, The American Heart Association.
8. Leech, C. B.: Streptococcus Viridans Endocarditis in Children, Am. J. M. Sc. 180: 621, 1930.

Abstracts and Reviews

Selected Abstracts

Green, H. D., Cosby, R. S., and Radzow, K. H.: Dynamics of Collateral Circulations. Am. J. Physiol. 140: 726, 1944.

A *cognate* system is defined as a vascular bed, the blood flow characteristics and primary artery and vein of which are being studied. It includes only those arterioles, capillaries, and veins which received blood from the cognate artery when the latter is receiving blood from the aorta or from a reservoir at a pressure equal to aortic mean pressure while all collateral arteries are being supplied from the aorta. Collateral systems include all arteries, capillaries, and veins which communicate with the cognate system by pre- and/or post-capillary anastomotic channels.

The magnitude of the exchange of blood across these anastomotic channels under various conditions was studied by measuring the flow of blood from a reservoir into the cognate artery at each of a series of pressures from 0 to above mean aortic pressure (a) while the collateral arteries were receiving blood from the aorta, and (b) while the collateral arteries were also being perfused from the reservoir at the same pressure as the collateral artery.

In experiments on the hind extremity of the dog, in which the collateral arteries were receiving blood from the aorta, and in which the resistance to flow in the arterial anastomotic channels was small in relation to that in the cognate capillary bed, it was observed that: (a) flow into the cognate artery at a perfusion pressure of 15 mm. Hg greater or less than the aortic mean pressure, differed from the flow through the cognate bed by 40 to 300 per cent; and (b) although the flow through the cognate bed was unchanged, the flow into the cognate artery under a constant head of pressure provided by a reservoir, increased 40 to 1900 per cent as a result of fall in the pressure in the collateral arteries such as might be produced by a decline of aortic pressure.

The effective collateral flow is defined as the rate at which blood will flow from the collateral beds through the anastomotic channels and thence through the cognate bed immediately after occlusion of the cognate artery. Measurement of the backflow from the distal end of the cognate artery provides a rough measure of the effective collateral flow. A better estimate of the effective collateral flow, with respect to the normal flow through the cognate bed at mean aortic pressure, is given by the ratio of the peripheral arterial pressure in the cognate artery, minus 20, to the mean aortic pressure. A still more accurate measure of the effective collateral flow is obtained by recording the flow into the cognate artery while perfusing the cognate and collateral arteries at a pressure equal to the peripheral arterial pressure (above), and comparing this with the flow through the cognate bed at mean aortic pressure. In various portions of the hind extremity of the dog, the effective collateral flow varied from 9 to 85 per cent of normal flow through the cognate bed.

Studies of the relationship of perfusion pressure to flow through the cognate bed may be satisfactorily accomplished in most vascular regions by perfusing the collateral arteries at the same pressure as the cognate artery. However, technical errors are very likely to occur whenever the flow into the collateral arteries is extremely large, or the anastomotic communications are very prominent.

In the presence of prominent venous anastomotic channels, outflow from the cognate vein may vary from 25 to 200 per cent of the flow through the cognate bed.

In flow studies in the distal part of extremities, the exchange of blood across both venous and arterial anastomotic channels may be effectively prevented by application of wire ligatures which tightly compress all structures except the cognate artery and vein and the nerves.

<div align="right">AUTHORS.</div>

Shipley, R. E., and Gregg, D. E.: The Effect of External Constriction of a Blood Vessel on Blood Flow. Am. J. Physiol. 141: 289, 1944.

The effect of an external constriction of a blood vessel in limiting blood flow has been considered with respect to the relationships of (1) vessel bore to volume flow, and (2) change in external to change in internal dimensions of the vessel. Experiments with an artificial system and in animals have led to the conclusions that:

The effect of a localized reduction in lumen area is primarily that of increasing the fluid friction (viscosity effect) at the site of the constriction, which results in an added "peripheral resistance" to the flow of blood and the rate of flow is thereby reduced.

The extent of flow reduction will vary in direct relation to the axial length of the constricted area, the velocity of flow, and the viscosity of the blood, and in inverse relation to the peripheral resistance of the bed and the lumen area of the vessel constriction. Since, with an intact blood vessel, it is impossible to determine all, or even most, of the above factors, an estimation of the flow reduction caused by a given constriction will be only as accurate as the estimated values placed upon the determining factors. Without the observer's knowledge, marked changes in the determining factors may occur, thereby making it impossible to predict within rather wide limits either the immediate or subsequent effects of a known constriction.

The findings presented here reveal no justification for the contention that a rather marked degree of external constriction is required to produce a significant reduction in flow through a vessel.

In comparison with other external constricting devices, the thermostromuhr cannot be regarded as having any less variable or unpredictable effect in limiting the rate of flow through the vessel to which it is applied.

<div align="right">AUTHORS.</div>

Koletsky, S., and Barnebee, J. H.: "Cardiac" or Congestive Cirrhosis. Pathologic and Clinical Aspects. Am. J. M. Sc. 207: 421, 1944.

Livers, the seat of prolonged and advanced passive hyperemia due to heart failure, sometimes show diffuse fibrosis and alteration of architectural pattern. These may properly be designated congestive cirrhosis. However, the degree of fibrosis and distortion of architectural pattern are considerably less than in well-developed Laennec's cirrhosis.

The main etiological factor is prolonged and severe hepatic venous stasis. Repeated episodes of decompensation favor the development of the lesion.

The most severe degree of fibrosis and architectural change occurred in patients with chronic constrictive pericarditis. The continual venous stasis in such cases suggests that the cirrhosis develops as a progressive process.

Congestive cirrhosis is relatively common in patients with rheumatic heart disease, both in those with mitral stenosis, and those with combined valvular lesions. It is less frequent in hypertensive patients and is uncommon or rare in other etiological forms of heart disease.

The clinical aspects of congestive cirrhosis do not provide adequate data for ante-mortem diagnosis.

Mayer, C. P., Lepera, L., and Pataro, F. A.: Character of the Precordial Ventricular Complex in ECG Tracings With Deviation of the Electric Axis to the Right. Rev. argent. de cardiol. 10: 245, 1943.

Right axis deviation and right ventricular strain have no characteristic precordial lead pattern. A deep S wave in all positions is often found in both cases and, in the latter, a negativity of T in CF_1.

AUTHORS.

Ash, R., Rubin, M. I., and Rapoport, M.: Electrocardiographic Variations in Acute Glomerulonephritis. Am. J. Dis. Child. 67: 106, 1944.

An analysis of the variations in serial electrocardiograms obtained from fifty children ill with a first attack of acute glomerulonephritis disclosed abnormalities in 72 per cent of the group. Abnormal variations were present in the tracings of 86 per cent of the children with clinical signs of heart failure, and in 57 per cent of those with negative or questionable cardiac findings. The incidence of clinically recognizable heart disease and of electrocardiographic variations was greater among patients in whom the blood pressure was high. At all levels of blood pressure, abnormalities in the electrocardiogram were noted more frequently than clinical evidences of cardiac involvement.

The most striking changes were observed in the T wave, consisting chiefly of flattening and inversion in one or more leads, although a transient increased amplitude of the T wave was also occasionally observed. Inversion of the T wave occurred late in the cycle and was not infrequently preceded, especially in Leads I and II, by a slightly depressed, upward bowed ST segment. Transient inversion of the T wave occurred as frequently in Lead III as in Lead I. The incidence of heart failure, however, was greater in association with inversion of the T wave in Lead I than in association with inversion of this wave in Lead III. In some instances isolated transient inversion of the T wave in Lead III may have been related to elevation of the diaphragm and change in position of the heart.

AUTHORS.

Campbell, A. M. G., Gibson, P. C., and Lane, C. R. T.: Auricular Fibrillation Late in the Course of Diphtheria. Brit. Heart J. 5: 183, 1943.

The authors recorded the occurrence of auricular fibrillation in a man, 39 years old, which arose during his convalescence from diphtheria. It lasted for 112 days, when it was stopped by quinidine. Except for his palpitation, it was unaccompanied by any symptoms referable to the cardiovascular system. It was associated with multiple peripheral neuritis, which preceded its onset by thirty-two days. There was a family history of arteriosclerosis, and some slight evidence of this in the patient himself.

AUTHORS.

Parsons, C. G.: Complete Auriculo-Ventricular Dissociation With High Ventricular Rate in Paroxysmal Tachycardia. Brit. Heart J. 5: 187, 1943.

A case of paroxysmal auricular tachycardia is described, in which there developed a spontaneous attack of A-V dissociation, with high auricular and ventricular rates amounting to a double tachycardia. The condition could be partly reproduced during attacks of auricular tachycardia by atropine, adrenalin, and carotid sinus pressure. The patient's heart was otherwise normal, and no drugs had been given. It is suggested that the condition is due to a form of heart block, the mechanism of which is allied to, but not identical with, the Wenckebach phenomenon.

AUTHOR.

Evans, W.: Triple Heart Rhythm. Brit. Heart J. 5: 205, 1943.

Triple rhythm is the cadence produced by the recurrence, in successive cardiac cycles, of three separate sounds. The chief purpose of this work has been to classify triple rhythm in accord with findings on clinical, radiological, cardiographic, and, sometimes, pathologic examination of the heart, in patients presenting this auscultatory sign. The investigation has shown the need for discarding the terminology hitherto in use for triple rhythm, and adopting one that is based on the clinical condition and avoids any preoccupation with the mechanisms of the extra sound. As soon as it becomes the custom to listen specifically for a sound in addition to the more familiar first and second heart sounds, triple rhythm will be found to be common, perhaps as common as dual rhythm in patients sent for examination of the heart.

When the position of the adventitious sound in the cardiac cycle was considered along with the clinical state of the patient in 270 cases with triple rhythm, it was possible to place them in three groups. As a rule, even under the handicap of fairly severe tachycardia, the position of the extra sound could be told by auscultation, aided by the clinical data, before phonocardiography was used for scientific support.

In the first group, consisting of 205 cases and comprising 125 healthy subjects and 80 patients with right ventricular heart failure, the added sound was the third heart sound occurring in early cardiac diastole. A simple triple rhythm is distinguished from that due to right heart failure by regarding the site of maximum audibility of the sound, the effect of posture upon the sound, and the health or disease of the heart. In the second group, the fourth heart sound is added during auricular systole and at the end of ventricular systole. There were sixty patients with this variety of triple rhythm. In fourteen of them, it was the outcome of delayed A-V conduction. In forty-six patients the extra sound appeared during left ventricular failure where auricular action, although probably not the direct cause of the sound, is essential for its production because it disappears with the onset of auricular fibrillation. In the third, and least important group, an extra sound is added in late systole.

Triple rhythm is a common auscultatory sign, and it can be of great aid in the diagnosis of cardiovascular disorder. It should be sought specifically in every case, and when found, the position of the supernumerary sound in the cardiac cycle should be traced, and its significance determined in the light of clinical findings and in accordance with some classification such as that here proposed.

<div align="right">AUTHOR.</div>

Marshall, R.: Persistent Truncus Arteriosus. Brit. Heart J. 5: 194, 1943.

A persistent truncus arteriosus was found, after death, in a boy, aged 13 years, who had always been cyanosed and breathless, and had suffered from hematemesis due to esophageal varices. The cardiac murmurs had been transient; there was no endocarditis, and death was attributed to congestive failure. Electrocardiogram, radiogram, and post-mortem findings are recorded.

<div align="right">AUTHOR.</div>

Goodof, I. I., and MacBryde, C. M.: Heart Failure in Addison's Disease With Myocardial Changes of Potassium Deficiency. J. Clin. Endocrinol. 4: 30, 1944.

A case of primary atrophy of the adrenal cortices, in which death was caused by cardiac failure, is reported. Foci of necrosis of cardiac muscle were present in the walls of all four chambers of the heart. Similar foci have been described in animals which have been given large doses of desoxycorticosterone acetate, or

which have been fed a diet deficient in potassium. It is believed that such changes may play a part in producing the cardiac abnormalities occasionally seen in patients receiving replacement therapy in Addison's disease.

<div align="right">AUTHORS.</div>

Thomson, H. W., and Feil, H.: Infarction of the Lateral Wall of the Left Ventricle. Pathologic and Electrocardiographic Study. Am. J. M. Sc. 207: 588, 1944.

Nineteen cases of left lateral infarction were found in 106 cases of myocardial infarcts, examined pathologically. Of these lateral infarcts, nine were recent. In these recent cases, the electrocardiograms of four (44.4 per cent) showed the pattern described by Wood, Wolferth, and Bellet.

Auricular fibrillation, or flutter, was found in five of these recent cases (55.55 per cent). This incidence may have been greater, actually, because all of the electrocardiograms showed auricular fibrillation or flutter to be temporary.

In the five recent cases without electrocardiograms diagnostic of lateral infarction, the changes were diagnostic of posterior and basal infarction in three instances. The other two cases showed auricular fibrillation, and in one of these the electrocardiogram showed slight but not diagnostic depression of the S-T segment in Lead IVR.

Two cases associated with infarction of the posterior and basal region of the left ventricle presented electrocardiograms dominated by the T_2 pattern. One case associated with anterior and apical infarction had left bundle branch block.

Seven cases of remote lateral infarction showed no characteristic pattern.

<div align="right">AUTHORS.</div>

Raab, W., and Soule, A. B., Jr.: Rationale and Results of Roentgen Treatment of the Adrenal Glands in Angina Pectoris. Am. J. Roentgenol. 51: 364, 1944.

Angina pectoris on effort, emotion, and so forth, is believed to be due, essentially, to the well-known, acutely anoxiating effect of adrenaline discharges from the adrenal glands upon the heart muscle, the sclerotic coronary arteries of which are unable to dilate adequately and thus to overcome the resulting myocardial anoxia. Clinical and experimental evidence is presented for this theory.

The state of abnormal irritability of the adrenal secretory mechanism which was found to be a characteristic of angina patients could be abolished through roentgen irradiation of the adrenal region without ensuing damage to the basic, normal function of the glands. This was demonstrated objectively by quantitative chemical hormone determinations in the blood before and after treatment, and by the normalization of pathologic electrocardiograms.

Of forty-two typical angina patients treated in Burlington, Vermont, with irradiation of the adrenal region, 74 per cent were either completely freed of their anginal complaints or, at least, improved for periods ranging between five and forty-five months with an average of two years up to the present.

Nine of the eleven unimproved patients had not received three series of roentgen treatments, and thus cannot be considered as definite failures.

No untoward side effects were noted except short episodes of nausea in a few cases.

Death occurred in seven out of the forty-two patients treated during the past four and one-half years.

<div align="right">AUTHORS.</div>

Cassels, D., and Steiner, P.: Mycotic Endocarditis: Report of a Case With Necropsy; Review of the Literature. Am. J. Dis. Child. 67: 128, 1944.

Studies of a sufficient number of cases of mycotic endocarditis are available to indicate that this condition represents a subdivision of the general category of subacute bacterial endocarditis. Frequently, as in bacterial endocarditis, valvular lesions from other infections are present previous to the onset of the endocardial infection. The clinical course appears to be indistinguishable from that of subacute bacterial endocarditis, and the laboratory findings, with the exception of blood cultures, are similar. In cases where the clinical findings suggest the diagnosis of subacute bacterial endocarditis, it is obvious that unusual organisms present in blood cultures should not be casually dismissed as contaminants, especially if these are present in repeated cultures. Likewise, negative blood cultures suggest the use of special mediums and especially long periods of incubation.

As interest in mycotic infection in man increases, it seems likely that mycotic endocarditis will be found to be more common than a survey of the literature indicates and that the variety of organisms responsible for the infection will be found to be diverse.

The case reported by the authors raises the question whether adequate treatment with sulfonamide compounds may not be of value in treatment in some instances of mycotic infection.

AUTHORS.

Feldt, R. H.: Sulfanilamide as a Prophylatic Measure in Recurrent Rheumatic Infection. A Controlled Study Involving 131 "Patient-Seasons." Am. J. M. Sc. 207: 483, 1944.

Sulfanilamide in small, daily doses was given to rheumatic children in the Cardiac Clinic of the Milwaukee Children's Hospital during the autumn, winter, and spring of 1941-1942 and 1942-1943. Altogether, eighty-nine patient-seasons were represented in the treated group and forty-two patient-seasons in the control series. No rheumatic recurrences appeared among the children who took sulfanilamide. There were three (7.2 per cent) major and minor recurrences among control patients. Questionable rheumatic episodes were observed with greater frequency in the control group. The incidence of positive beta hemolytic streptococcus throat cultures was approximately the same in the two groups. Manifestations of sulfanilamide toxicity were neither frequent nor severe. Sulfanilamide is recommended as a relatively safe and effective prophylactic measure against recurrent rheumatic infection.

AUTHORS.

Shank, R. E., Coburn, A. F., Moore, L. V., and Hoagland, C. F.: The Level of Vitamin A and Carotene in the Plasma of Rheumatic Subjects. J. Clin. Investigation 23: 289, 1944.

The level of vitamin A and carotene in the plasma is related to the intake of vitamin A in the diet of rheumatic subjects.

Irrespective of the concentration prior to the onset of disease activity, there is a fall in the level of vitamin A in the plasma with the development of acute rheumatic fever. The concentration of carotene in the plasma is not significantly changed during rheumatic attacks.

The degree of decrease of vitamin A in plasma varies directly with the intensity of the rheumatic attack. In severe attacks, concentrations in the plasma varied between 0 and 70 I.U. of vitamin A per 100 c.c. plasma.

Patients with rheumatic fever show delayed or decreased absorption of vitamin A, or metabolize it in an abnormal manner.

AUTHORS.

Auerbach, O., and Stemmerman, M. G.: The Development of Pulmonary Tuberculosis in Congenital Heart Disease. Am. J. M. Sc. 207: 219, 1944.

A study has been made of thirteen patients who had congenital heart disease and contracted pulmonary tuberculosis. Upon seven of these patients post-mortem examinations were performed. The most common congenital defect was pulmonary stenosis, which was present in all cases which came to autopsy, implying a certain predisposition of these patients to tuberculosis.

A composite picture of the typical case, including clinical, physiologic and pathologic studies, has been presented. From this material it may be concluded that the pulmonary tuberculosis runs a course typical of that disease, irrespective of the cardiac lesion. The functioning of the defective cardiac system is affected very little by the superimposed respiratory infection.

In view of this observation, together with the fact that these patients succumbed to pulmonary involvement rather than failure of the defective cardiovascular system, active treatment of tuberculosis is recommended. Pneumothorax induced in 5 of the patients did not lead to congestive heart failure in any instance. The importance of other surgical forms of collapse therapy for these patients has been discussed.

AUTHORS.

Howell, T. H.: Heart Failure in the Aged. Brit. Heart J. 6: 20, 1944.

The causes and forms of heart failure in seventy-five old persons are described.

The commonest causes of failure were high blood pressure, disease of the coronary artery, and myocardial toxemia.

In 13 per cent of the cases, the cause of heart failure remained uncertain after repeated clinical examination.

The occurrence of ''forward'' heart failure, with peripheral ischemia is described, and the importance of arteriosclerosis in producing circulatory failures is stressed.

AUTHOR.

Sensenbach, W.: Effects of Unilateral Nephrectomy in Treatment of Hypertension: An Evaluation. Arch. Int. Med. 73: 123, 1944.

Only five of the seventy-five cases of hypertension taken from the literature meet the requirements for cure after nephrectomy. Approximately one-third of the patients had a fall in blood pressure in normal levels, but had been followed for less than two years at the time their cases were reported. One-third had a reduction in blood pressure, but remained hypertensive, while in one-third the blood pressure was unchanged or increased in severity.

The most common pathologic condition in the removed kidneys was chronic pyelonephritis.

A two year follow-up period is necessary before hypertension can be considered cured by nephrectomy.

Cases in which unilateral nephrectomy is indicated for hypertension are rare, and there is need for more careful selection of such cases.

The removal of a kidney, if it retains any function at all, is likely to increase the severity of the hypertension, rather than to improve it. This is true even though the function of the opposite kidney is entirely normal.

The usual tests of renal function may at times be unreliable, and in the light of this fact, special care and consideration must be given to evaluation of the function of each kidney before nephrectomy is performed.

The age of the patient and the duration of the hypertension are additional factors of importance in the selection of suitable cases for nephrectomy in the treatment of hypertension.

AUTHOR.

May, J.: The Frei Reaction in Arteriopathies of the Lower Extremities. Rev. argent. de cardiol. 10: 257, 1943.

The Frei reaction, which is considered by the author as specific for poradenitis, was tested in patients with arterial diseases of the lower limbs. It is recommended to use 0.1 to 0.3 c.c. of a good antigen, so that cases with slight allergy do not escape detection.

Twenty-two patients were studied: two with a history of syphilis were Frei positive. Of the other twenty, without syphilitic antecedents, eleven had Buerger's disease and, of these, seven were Frei positive; and nine had arteriosclerosis obliterans. Two of these were senile and Frei negative; the other seven (ages between 39 and 60 years) were Frei positive.

Treated with sulphamides (2 grains per day) and emetic tartrate (0.02 grains on alternate days) complete reintegration was obtained in the two syphilitic patients. In the thromboangiitis obliterans cases two were cured, a few were improved, and the treatment failed in others. In four cases of arteriosclerosis obliterans a slight improvement was obtained.

AUTHOR.

Sheehan, J. F.: Foam Cell Plaques in the Intima of Irradiated Small Arteries. Arch. Path. 37: 297, 1944.

An uncommon, or, at least, rarely described, lesion of small arteries (100 to 500 microns in external diameter) has been observed in several irradiated organs. The lesion consists of a plaquelike thickening of the intima, due to a collection of foam cells alone or of foam cells mixed with various other cells, fluid, fibrin, or hyaline material, between the endothelium and the internal elastic membrane. Pathologic changes may be found in the adjacent internal elastic membrane, media, and adventitia, but these structures are often normal. The plaque may cause marked narrowing, or even occlusion, of the lumen of the vessel. Thrombosis, fibroblastic proliferation of the intima, or deposition of elastic tissue in the thickened intima seldom result.

These foam cell plaques have been found in the arteries of organs subjected to roentgen therapy only, radium therapy only, or to both combined.

The plaques probably result from migration into the intima from the blood stream of lymphocytes and monocytes and subsequent transformation of these into foam cells by their ingestion of lipids which have been freed by the dissolution of red cells in the intima, or which have accumulated in the intima after passage across portions of the endothelium rendered more permeable than normal by irradiation.

The foam cell plaques in irradiated small arteries closely resemble the early lesion of atherosclerosis.

AUTHOR.

Dalton, J. W., and Nuzum, F. R.: The Effect of Sodium Thiocyanate on the Pressor Action of a Renin-Like Substance. Am. J. Physiol. 141: 415, 1944.

By subcutaneous injection or by mouth, sodium thiocyanate will minimize the pressor effect of unit amounts of a renin-like substance when injected intraperitoneally into normal and sensitized rats.

There is some indication that sodium thiocyanate does not act directly to perform this function but that it may activate some other mechanism in the body which is not so easily dissipated as sodium thiocyanate and which will continue to eliminate the pressor effect.

AUTHORS.

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

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The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

Executive Committee.

Original Communications

MEASUREMENTS OF THE CIRCULATION IN A PATIENT WITH MULTIPLE ARTERIOVENOUS CONNECTIONS

J. ALLEN KENNEDY, M.D., AND C. SIDNEY BURWELL, M.D.[*]

BOSTON, MASS.

INTRODUCTION

THIS communication presents observations on the circulation of a young man with multiple arteriovenous fistulas in his forearm. It deals with the heart rate, the arterial blood pressures, the venous blood pressures, the volume of the arm containing the fistulas, the oxygen content of arterial and venous blood, the circulation times, the oxygen consumption, the blood volume, the output of the heart, the volume of blood flowing through the fistula, and the work of the heart. Some of the observations are not new, and serve only to confirm well-established facts. Others, however, deal with aspects of the circulation which have not been thoroughly studied in human beings with this disorder of the circulation. Particular attention is directed to the cardiac output and the total blood volume.

Several instructive investigations of the circulation in cases of arteriovenous fistula have been recorded: Reid;[1, 2] Lewis and Drury;[3] Harrison, Dock, and Holman;[4] Holman;[5-7] Ellis and Weiss;[8] Laplace;[9] Gibbon and Churchill;[10] Reid and McGuire;[11] McGuire, Hauenstein, Stevens, and Sharretts;[12] and others. Some of these articles, which bear particularly on the cardiac output or the blood volume, may be considered briefly.

Lewis and Drury[3] observed a man with a right-sided femoral arteriovenous fistula. They found no change in the general venous pressure upon opening and closing the fistula, and their plethysmographic observations indicated that, upon compression of the fistula, there was an increased flow of blood to both the left arm and left leg. These two observations were used as evidence for their conclusion that the output of the heart remained practically unaltered, whether the communica-

tion was open or closed. To quote: "To sum up, it seems to be an unavoidable conclusion that the sole change of importance occurring in the circulation of blood on closing the arteriovenous aneurysm was that that portion of blood, hitherto passing through the aneurysm directly to the vein, was now directed to the capillaries, and through these reached the veins; and that by this mechanism the filling of the veins and the output of the heart were maintained at what was practically a constant point."

Lewis and Drury[3] also recorded observations made on dogs with surgically produced arteriovenous fistulas. They found that femoral vessel anastomosis "is apparently without influence upon the general venous pressure. When the iliac vessels were used the venous pressure may or may not change." The maximum rise observed by them was 9 mm. of water. They measured the output of the heart by a recording ventricular volume apparatus, and found increases in cardiac output only in those cases in which rises of venous pressure were observed, that is, only when there were anastomoses of larger vessels. They concluded that cardiac output and venous pressure run hand in hand.

Harrison, Dock, and Holman,[4] using the "direct Fick" method, presented evidence that, with surgically produced arteriovenous fistulas in dogs, the cardiac output was increased by the presence of the fistula. All four of their dogs had an increased output after the production of the fistula, and these outputs again approached their preoperative levels after closure of the fistula surgically. When the fistula was open the cardiac output was increased by almost 100 per cent.

Gibbon and Churchill[10] induced arteriovenous fistulas in cats for the purpose of studying the increased volume flow of blood through the lungs. They used the Fick method, and found the output of the heart increased on opening the fistula. The increase varied from 24 per cent to 59 per cent in five different cats.

Gley and Gomez[12] made observations on one dog, using the carbon dioxide, arteriovenous difference, and the Fick principle, and found the cardiac output approximately doubled with the fistula open.

Reid and McGuire[11] studied the effects of large fistulas between the abdominal aorta and the vena cava in dogs. The cardiac output, measured by the direct Fick method in three dogs, was increased over 100 per cent (average) in acute experiments. The blood volume was measured, and, they concluded, "our studies, thus far, fail to confirm the observations of Holman and others, who have reported a large increase in the blood volume in cases of arteriovenous aneurysms."

In addition, they found that the circulation time, measured by the sodium cyanide method, was longer than usual if a vein distal to the fistula was used, and shorter than usual if one proximal to the fistula was utilized. The flow of blood through the vena cava, as measured by a Venturi meter, was greatly increased by the presence of a fistula.

McGuire, Hauenstein, Stevens, and Sharretts[12] reviewed and evaluated most of the evidence concerning the circulatory changes caused by arteriovenous fistulas. They point out that there is good agreement on many of the observations, but that several points are still controversial, and among these are the changes in cardiac output, blood volume, and the venous pressure proximal to the fistula.

The cardiac output in the presence of an arteriovenous fistula has been measured in human beings by several workers. Ellis and Weiss[8] recorded observations made with the acetylene method of Grollman.[14] Their results indicated no considerable change in cardiac output, but the authors carefully point out the possibility that recirculation may have occurred during the rebreathing period, and that their figures for the output when the fistula was open may be too low.

Smith,[15] using the method of Field, Bock, Gildea, and Lathrop,[16] realized that the factor of recirculation was important, and consequently obtained gas samples within twelve to fourteen seconds in an attempt to minimize the effect of recirculation.[17] He made twenty-three cardiac output determinations over a period of three months on a patient with a femoral arteriovenous fistula who also had congestive heart failure and hypertension. Before surgical elimination of the fistula the cardiac output averaged 8.95 liters per minute. During the two weeks after the operation the cardiac output averaged 3.76 liters per minute. Two months after operation, when the signs of the fistula had reappeared, the cardiac output averaged 6.77 liters per minute.

Laplace[9] recorded observations on a patient with a femoral arteriovenous fistula and moderate heart failure. He used the Starr and Gamble[18] modification of the ethyl iodide method in making determinations of the cardiac output with the fistula open and closed. He also utilized the acetylene method of Grollman for determinations of the output with the fistula closed. With the fistula open he found that the average cardiac output was 5.15 liters per minute (cardiac index, 2.64); with the fistula closed by compression, the average cardiac output was 4.13 liters per minute (cardiac index, 2.12). After operation for elimination of the fistula the average cardiac output was 3.91 liters per minute (cardiac index, 2.02). He concludes that an increased minute volume is a compensatory mechanism when the leak is of significant size and the heart is sufficiently competent.

Horton,[19] in a brief communication, stated that the cardiac index was higher than normal by the acetylene method. The factor of recirculation was not mentioned.

In measuring the cardiac output the factor of recirculation is of sufficient importance to cast doubt on results obtained by the acetylene method unless certain precautions are observed. Those obtained by the ethyl iodide method seem acceptable.

There are several reports of observations on the blood volume in the presence of an arteriovenous fistula. The blood volume was investi-

gated by Holman[6] in dogs. By the method of Hooper, Smith, Delt, and Whipple,[20] he found the blood volume considerably increased in the presence of large, surgically produced, arteriovenous fistulas. He concluded that the increase in blood volume roughly followed the size of the fistula. Ellis and Weiss[8] found that the blood volume was within normal limits in a patient with a femoral arteriovenous fistula; they used the Keith, Rowntree, and Geraghty technique.[21]

In a more recent report, Holman[7] found that the blood volume of two young dogs was increased 250 c.c. and 590 c.c., respectively, as compared with a litter mate control, at an interval of about three months after the establishment of large fistulas. From the protocol it seems possible that the dog with the largest increase in blood volume also had congestive heart failure. Blood volume determinations on several patients before and after operative closure of the fistula showed a consistent drop after operation. The method by which the blood volume was estimated is not mentioned, although a dye method was used. He believes that the increase in blood volume is in proportion to the increase in the vascular bed caused by the fistula.

Reference has been made earlier to the work on blood volume done by Reid and McGuire,[11] and by McGuire, Hauenstein, Stevens, and Sharretts.[12] Gibson and Evans[22] have pointed out the difficulties in blood volume determinations involving the use of red dyes which many of these methods employed, and Kennedy and Millikan[24] and Gregersen, Gibson, and Stead[25] have summarized these difficulties.

The study of our patient adds to this available information regarding changes in cardiac output, blood volume, and other dynamic aspects of the circulation.

REPORT OF THE PATIENT

A 19-year-old boy entered the surgical service of the Peter Bent Brigham Hospital in May, 1936, complaining of an enlarged left forearm. Ten years before, at the age of 9 years, he had fallen out of a swing and bruised his left forearm. During the several weeks after the injury the arm was greatly swollen, and, soon afterward, large, dilated veins began to appear near the site of the injury. (It is not known whether the subcutaneous tissue was discolored at the time of the injury.) The veins became more prominent and the left forearm larger during the succeeding years. This change was associated with a sense of heaviness and awkwardness, but with no muscular disability.

On physical examination the only abnormalities were those observed in relation to the left arm and the cardiovascular system. The left forearm was markedly enlarged; the circumference measured 8 cm. greater than the normal arm. The veins of the forearm were tense and greatly dilated, and were most prominent over the extensor surface, where they formed a tortuous venous plexus which pulsated, both visibly and palpably. The pulsation was synchronous with the radial arterial pulse. There were both a continuous thrill and a loud continuous murmur over the dilated plexus of veins and in the antecubital fossa. Both thrill and murmur were accentuated with each systole, and both ceased abruptly when the brachial artery above the elbow was occluded.

The heart rate was somewhat rapid and a soft systolic murmur was present over the precordium. This murmur could be traced outward along the course of the left brachial artery to the region of the distended veins, where it was found to be inseparable from the systolic phase of the murmur described as heard there. This precordial murmur, in spite of its location, was considered to be an extracardiac, transmitted murmur, and not generated within the heart. The heart was not enlarged, and there were no signs of cardiac failure or even of limitation of cardiac reserve. The vital capacity was 4,650 c.c.

Fig. 1.—Infrared photograph of right and left forearms, showing relative size and venous distension.

There was no anemia, the urine was normal and the blood Wassermann reaction was negative.

A photograph of the left forearm, showing its size (relative to the right) and the visible veins on its surface, is shown in Fig. 1. Arteriograms of the affected vessels are shown in Fig. 2.

The signs were those of a large arteriovenous connection, and this diagnosis was made. As will be seen, many of the special measurements gave support or added detail to that diagnosis.

OBSERVATIONS ON THE CIRCULATION

These measurements will be described under the following headings: (a) heart rate, (b) arterial blood pressure, (c) arm volume, (d) blood volume, (e) venous blood pressure, (f) circulation time, (g) oxygen content of the blood in the veins, and (h) cardiac output. The observations were made by accepted methods (which will be mentioned) and, unless otherwise stated, under so-called "basal" or "standard" conditions. It was hoped that it might be possible to study these functions both in the presence of the fistula and after its cure by operation, but, unfortunately,

Fig. 2.—Arteriogram, showing prompt entrance of opaque substance into venous plexus.

the patient turned out to have multiple fistulas of the left forearm, and several operations have not restored to integrity the circulation in this arm. Therefore, most of the observations refer to the situation as it was when the patient first came under observation.

a. Heart Rate: The average basal heart rate before operation was 82 per minute; on several occasions it fell below 80 per minute. Sudden

closure of the fistula (compression by inflation of a blood pressure cuff) was followed by immediate slowing of the heart rate by an average of 18 beats per minute (from 14 to 23 on separate observations). It was found that rather vigorous carotid sinus stimulation on the right side was followed by slowing of the heart to approximately the same rate as that following closure of the fistula. Stimulation of the left carotid sinus elicited no such response. Simultaneous stimulation of the sinus *and* closure of the fistula were followed by the same degree of slowing of the heart rate as either one performed separately.

Electrocardiograms taken under basal conditions were normal. Tracings taken after closure of the fistula and after carotid sinus stimulation showed slowing of the rate, but no change in the form of the complexes. Slowing of the heart rate upon closing the fistula was observed after exercise as well as under basal conditions, the only difference being that the slowing was of lesser extent.

b. Arterial Blood Pressure (at rest and recumbent): Before the first operation the blood pressure was 110/0 in the left arm, 102/60 in the right arm, 124/82 in the right leg, and 128/78 in the left leg. These values represent averages of several measurements. After quickly closing the fistula by occluding the left brachial artery (mercury manometer at 160 mm.), the diastolic pressure in the right arm was elevated 10 to 15 mm. The systolic pressure usually was elevated only a few mm. under these circumstances.

c. Arm Volume: The volume of each forearm and hand was measured by its displacement of water. It was found that the volume of the left forearm was greater by 595 c.c. (average of two measurements). A large part of the increased volume was probably due to blood in the overfilled veins.

d. Blood Volume: The circulating blood volume was ascertained by the method of Gibson and Evans*[22] (see also Gibson and Evelyn[23]). This method employs a blue azo dye and is more accurate than the red dye method. The results of the blood volume measurements are shown in Table I. Before the first operation the total blood volume was 6,770 c.c. According to the data of Gibson and Evans,[26] the theoretical normal blood volume of this patient was 5,475 c.c. His blood volume was therefore 24 per cent greater than the expected normal. After the operations his blood volume fell to about 5,800 c.c., which is about 6 per cent greater than the theoretical normal. Six months later it was again observed at this level, but during the following five months it fluctuated, reaching the preoperative level twice. We are not able to offer an explanation for the fluctuations in volume. It is to be noted that the fistula was never permanently closed, although there were times after operation when the thrill and murmur were considerably lessened.

e. Venous Blood Pressure: The venous pressure was measured by the direct method of Lyons, Kennedy, and Burwell.[27] A small amount

of procaine was used to anesthetize the tissues overlying the vein before each measurement. The zero point of the manometer was set 10 cm. anterior to the skin of the back with the patient lying flat on his back. With the fistula open the pressure in the right antecubital vein was 95 mm. of water, and in the right femoral vein was also 95 mm. Occluding the fistula for several minutes had no measurable effect on the pressure in the right arm and leg veins.

TABLE I

OBSERVATIONS ON THE BLOOD VOLUME AND RELATED DATA

	TOTAL BLOOD VOLUME (C.C.)	PLASMA VOLUME (C.C.)	HEMATOCRIT PER CENT CELLS AVERAGE OF 3 OR 4 SAMPLES	BODY WEIGHT (KG.)	SURFACE AREA (SQ. M.)	AVERAGE NORMAL TOTAL BLOOD VOLUME (C.C.*)	PER CENT OF NORMAL TOTAL BLOOD VOLUME
5/21/36	6,770	4,000	40.9	65.8	1.84	5,475	+24
6/ 4/36	First operation						
10/ 1/36	5,850	3,215	45.1	65.3	1.84	5,475	+7
10/7 to 24/36	Second operation (series)						
12/23/36	5,770	3,325	42.4	65.9	1.84	5,475	+5
4/15/37	6,120	3,500	42.8 ·	68.8	1.88	5,650	+8
4/29/37	7,020	4,070	41.9	68.8	1.88	5,650	+24
6/ 9/37	6,040	3,340	44.7	67.0	1.86	5,550	+9
9/16/37	6,880	3,550	48.4	67.5	1.86	5,550	+24

*Data for normal blood volume from Gibson and Evans.[26]

In the left arm (the one containing the fistula) the pressures were elevated. In veins of the dilated plexus on the dorsum of the forearm, pressures of 295 to 455 mm. were observed. There was a marked pulsation in these veins that was transmitted to the fluid in the manometer, where an oscillation of about 5 mm. was seen; the increase in pressure was synchronous with the radial pulse. In other veins a short distance from the dilated plexus the pressure was 175 mm., and in veins on the arm several centimeters proximal to the elbow, still more distant from the dilated plexus, the pressure was 120 mm. Thus, there was a fall in the pressure with increasing distance away from the fistula (Fig. 3).

In order to ascertain whether the elevation of pressure in the abnormal arm was caused by the fistulous leak or was of central origin, the venous pressure was measured simultaneously in the right femoral vein and the left cephalic vein at the mid-arm (halfway between elbow and shoulder). The cuff of a mercury arterial blood pressure manometer was placed about the arm just proximal to the elbow, but distal to the site of the needle of the venous pressure manometer, so that the venous channel from the superior vena cava outward to the blood pressure cuff was unobstructed. The cuff was then inflated to a pressure of 150 mm. Hg, thereby stopping the flow of blood through both the arteries and veins below that level. Before thus interrupting the flow through the fistula, the pressure in the femoral vein was 93 mm., and, in the left cephalic vein, 145 mm. After occlusion by the manometer cuff, the

pressure in the femoral vein was 92 mm., and, in the cephalic vein, 90 mm. It is clear from this observation that the pressures in the superior and inferior caval systems were equal when the fistulous opening was shut off, and that the elevation of pressure in the veins of the left arm was due to the leak from the arterial to the venous channels in a localized area.

The venous pressure was increased near the fistula, but not in the veins of the body generally. In the right (normal) arm and right leg the venous pressure was normal and equal, and in neither was the pressure changed by opening and closing the fistula temporarily. In the left arm, the pressure was elevated in veins as near the heart as measurements could be made in (that is, in the cephalic vein near the shoulder, which was 25 cm. from the fistula).
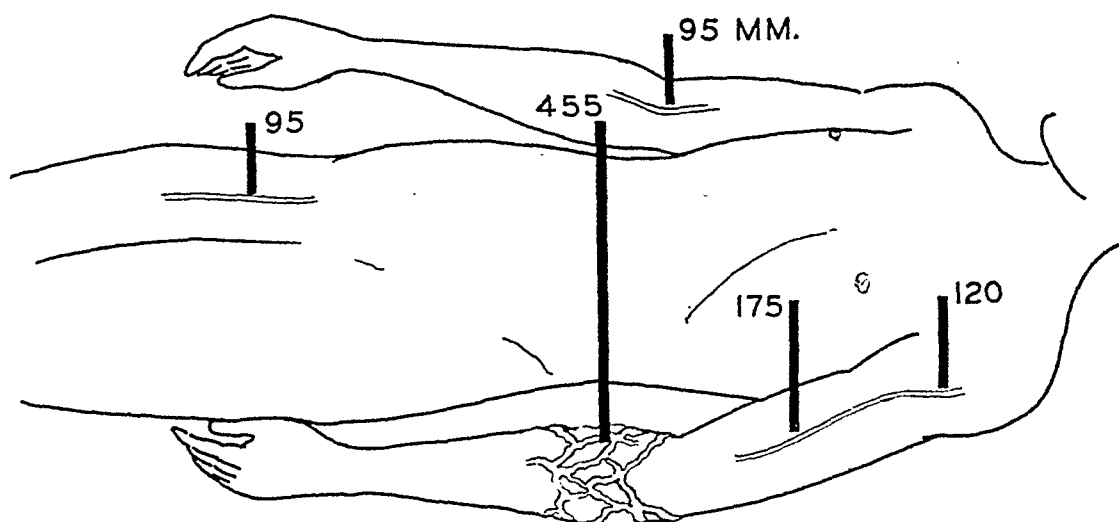
Fig. 3.—Diagram showing normal venous pressure in the right arm and right leg, and elevation of the venous pressure in the vicinity of the arteriovenous fistula.

f. Circulation Time: The circulation time was measured by intravenous injection of sodium dehydrocholate (Decholin). The circulation time from the right antecubital vein to the tongue (i.e., in the normal arm) was 22 seconds, 17 seconds, and 18 seconds on three occasions. The circulation time from one of the large dilated veins of the left forearm to the tongue was much more rapid, namely 12.5 seconds, 11.5 seconds, and 12.5 seconds on three separate occasions. From the femoral vein, 2 inches below the inguinal ligament, to the tongue, the circulation time was 19 seconds on two occasions.

The circulation time from veins of the right arm and right leg to the tongue was normal, and *remained the same* whether the fistula was open or closed. Thus, the speed of circulation of venous blood in parts of the body not in the vicinity of the fistula was not influenced by temporary closure of the fistula.

g. Oxygen Content of Venous Blood: The oxygen content of blood drawn from veins of the right arm, right leg, and left wrist (distal to the fistula) was at a level of 75 to 80 per cent saturation. Blood drawn

from veins nearer the fistula was more completely saturated. The blood in the veins of the dilated plexus on the dorsum of the left forearm had an oxygen saturation of 94 per cent, and that from veins a few centimeters from the dilated plexus, a saturation of 90 to 93 per cent. Arterial blood drawn from the femoral artery was 94.2 per cent, 94.7 per cent, and 95 per cent saturated with oxygen on three separate occasions.

It is clear from these observations that blood drawn from veins near the fistula was at an oxygen saturation closely approaching that of arterial blood.

h. Cardiac Output: There are inherent difficulties in measuring the output of the heart when the circulation is affected by the presence of an arteriovenous fistula of considerable size. It is generally agreed that the acetylene method of Grollman[14] is an acceptable method for cardiac output measurements on normal persons, and it was desired to use this method. In using it, there are two important conditions that must be fulfilled. The first is that there must be a thorough mixing of the gases in the lung-bag system before the gas samples are taken. The second condition is that all gas samples must be taken before any considerable recirculation takes place, that is, before blood which leaves the lungs containing acetylene returns to the lungs again. If either of these conditions is not fulfilled, the observed arteriovenous oxygen difference will be incorrect. With sufficient training the first is not difficult. In applying this method to this patient, it was of importance to know the actual time required for recirculation of the blood, that is, for blood to leave the lung capillaries, pass through the fistulous opening, and return again to the lung capillaries.

For convenience in studying, the recirculation time was divided into two separate periods: first, the time required for the blood to pass from the lung capillaries to the fistula, and, second, from the fistula back to the lung capillaries. These two periods were measured separately.

To measure the fistula-to-lung circulation time, the ether method of Hitzig[28] was used. A large vein of the dilated plexus on the left forearm was selected; it was the one in which the highest per cent of oxygen saturation and the highest venous pressure were observed. Two separate measurements (5.2 seconds and 6.5 seconds) averaged 5.9 seconds.

The lung-to-fistula time was measured with more difficulty. A substance was sought that could be inhaled, would pass into the blood, could be recovered at the periphery, and be recognized in a small volume of blood. It was found after many trials with several substances that carbon monoxide would satisfy these criteria. The measurement of the lung-to-fistula time was made in the following way: Three hundred cubic centimeters of freshly made carbon monoxide gas, mixed

with 600 c.c. of air, were placed in a rubber bag to which an airtight, two-way, metal valve and rubber mouth piece were attached. A number 18 lumbar puncture needle was then inserted into the vein at the same time previously used for ether injection. A brisk flow was obtained because of the elevated pressure. The end of the needle was then held in such a position that the blood ran directly into each of a succession of small glass tubes which contained 0.5 c.c. of aqueous potassium oxalate solution (0.5 c.c. of solution containing 1 mg. of potassium oxalate). The tubes were attached to the rotating drum of a kymograph which was so regulated that each tube passed the end of the needle in one second (see Fig. 4). In this way blood was collected.
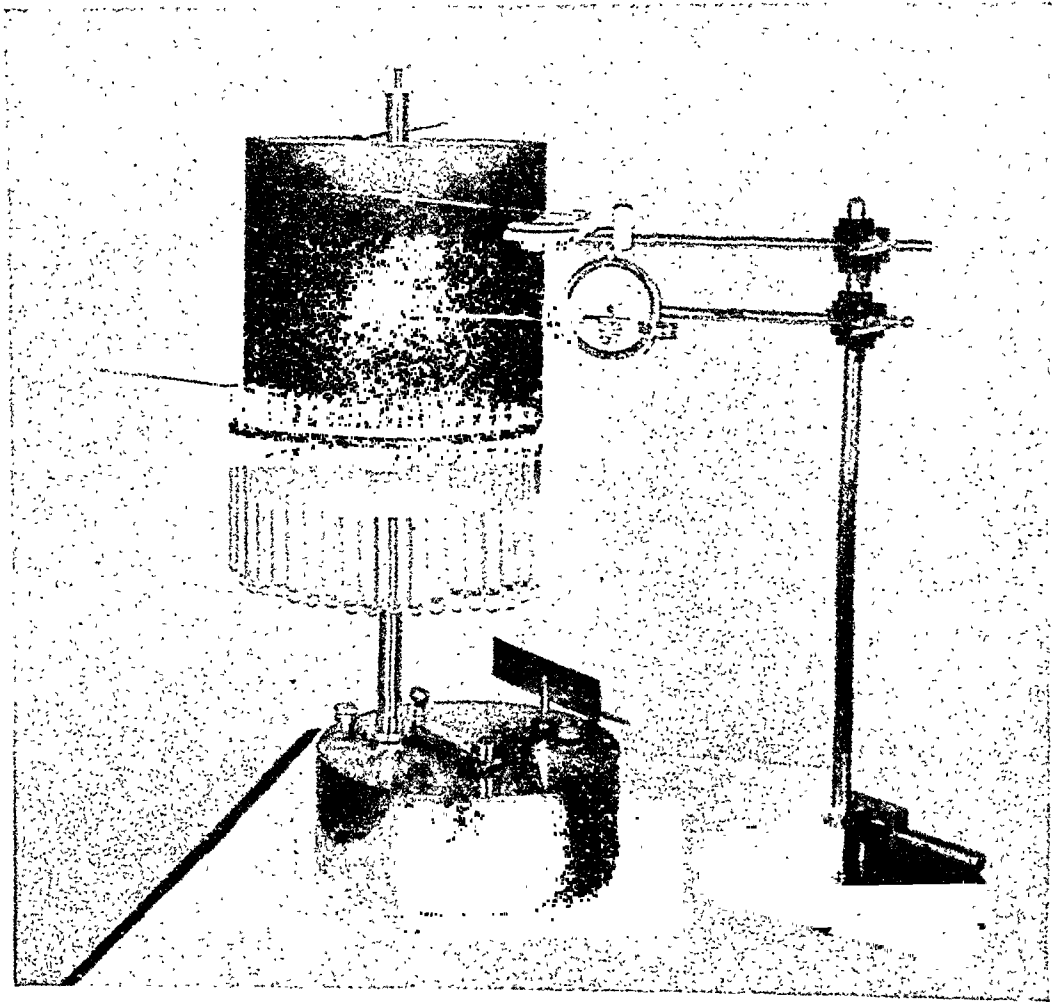
Fig. 4.—Arrangement of tubes for collecting samples of blood at one-second intervals.

in the tubes from the vein at one-second intervals. After six to eight tubes had rotated past the needle, each collecting a one-second sample of blood to use as controls, the valve was turned at a given signal and the subject quickly inspired the contents of the bag and held the inspiration for twenty to thirty seconds. The time of inspiration was recorded on the drum. This method of collecting blood samples at short intervals is similar to that introduced by Moore, Kinsman, Hamilton, and Spurling.[31] Such samples were collected for six to eight seconds be-

fore, and twenty to twenty-five seconds after, inhalation of carbon monoxide. These tubes were then removed from the drum, shaken slightly to mix and prevent clotting, and then immediately examined for the presence of carbon monoxide hemoglobin.* This was done by means of a photoelectric cell and a specific light filter. The filter is one of a series of specific filters which pass only a narrow band of wave lengths of light, and has been used to study compounds of hemoglobin by Evelyn.[29, 30] With this device, minute traces of carbon monoxide hemoglobin can be detected. In one of two separate observations the carbon monoxide hemoglobin appeared first in the tube collecting blood during the sixth to seventh seconds after inhalation, and, in the second observation, in the tube collecting blood during the fifth to sixth seconds. These two observations averaged six seconds. Thus the total time required for recirculation from the lungs through the fistula and back to the lungs was approximately twelve seconds. Therefore, if, in using the acetylene method, the gas samples were collected within twelve seconds after the beginning of rebreathing, recirculation should not have occurred in sufficient amount to cause significant error, and the observed arteriovenous oxygen difference should be valid.

The three-sample, acetylene method of Grollman was used throughout. The subject was thoroughly trained in the technique of rebreathing, and was able to inhale and exhale, completely, 2,000 c.c. of acetylene mixture at a rate of more than once per second. Usually the gas in the lung-bag system was mixed in six seconds. Gas samples were taken at six, nine, and twelve seconds, and two separate arteriovenous oxygen differences were obtained. To be acceptable, these two must agree within about 10 per cent.

The cardiac output was measured many times under these conditions, and the observations are presented in Table II. (All observations were made with the subject under basal conditions, that is, fasting for at least twelve hours and having remained completely relaxed in a quiet room for at least forty minutes before the observation.)

It is clear from these data that the output of the heart was greatly increased when the fistula was open. The theoretical normal value for this man's cardiac output, assuming a normal cardiac index of 2.2 per square meter of body surface, was about 4,100 c.c. per minute. This theoretical normal value corresponds well with the actual cardiac output of 3,960 c.c. per minute which was observed after closure of the fistula for forty-five seconds.

The observation on June 26, 1936, may not be a true measurement of the cardiac output with the fistula "closed," for an insufficient lapse of time may have been allowed between closure of the fistula and beginning of rebreathing to allow the circulation to become adjusted under these

TABLE II

OBSERVATIONS ON THE CARDIAC OUTPUT AND RELATED DATA

DATE	OXYGEN CON- SUMP- TION PER MINUTE (C.C.)	BASAL META- BOLIC RATE (%)	BASAL PULSE RATE PER MINUTE	ARTERIO- VENOUS OXYGEN DIFFER- ENCE	CARDIAC OUTPUT PER MINUTE (C.C.)	CARDIAC INDEX LITERS PER SQ. M.	SYSTOLIC OUTPUT PER BEAT (C.C.)
				Fistula Open			
6/ 3/36	230	−11	81	38.9 38.3	5,950	3.2	79
6/ 4/36	First operation						
7/ 3/36	248	−5	87	47.6 48.1	5,220	2.8	60
9/28/36	254	−3	84	52.2 50.6	4,950	2.7	59
10/7 to 24/36	Second operation						
11/27/36	221	−12	81	42.2 42.9	5,190	2.9	64
12/24/36	246	−7	80	48.0 54.7	4,800	2.6	64
2/10/37	235	−7	82	57.3 53.5	4,240	2.2	51
2/23/37	232	−10	77	51.1 49.0	4,630	2.4	68
4/13/37	247	−4	74	58.1 59.1	4,220	2.2	62
6/ 8/37	238	−6	81	54.7 55.4	4,320	2.3	55
				Fistula Closed			
6/25/36*	241‡	−8	74	55.4 53.9	4,410	2.4	51
10/ 5/36†	227‡	−12	74	56.9 58.2	3,960	2.1	54

*Fistula closed for about twenty seconds before rebreathing begun.
†Fistula closed for forty-five seconds before rebreathing begun.
‡Oxygen consumption measured with fistula closed, throughout.

conditions. However, the time elapsing before rebreathing in the observation made Oct. 5, 1936, was measured accurately with a stop watch, and the result in this case is a true measure of the cardiac output with the fistula closed.

Before operation his cardiac output was 5,950 c.c. per minute. During the months after operation his output gradually diminished, and the signs of the fistula were less prominent until, eight months after the first operation, his cardiac output was within normal limits for the first time. At this time the physical signs of the fistula were minimal, although still present. Since that time there have been indications that fistulous openings have become re-established. On June 7, 1937, the veins of the plexus were dilated, but did not pulsate, and no thrill was present; however, the bruit seemed to be louder than before. Temporary occlusion of the left brachial artery slowed the heart rate 8 beats per

minute. During this period, when the physical signs were changing in a way which suggested a recurrence of the arteriovenous leak, the cardiac output did not change significantly.

Basal Metabolism.—The oxygen consumption under basal conditions ranged from 221 to 254 c.c. per minute, which represented basal metabolic rates of minus 12 per cent to minus 3 per cent. The oxygen consumption was not significantly changed by opening or closing the fistula.

Operations.—On several occasions during the period of our observations, attempts were made to close the fistula surgically. None of these succeeded, although several abnormal communications were closed. It is believed that the amount of blood flowing through the abnormal channels was greatly reduced by operation, but that there still remained a fistulous opening or series of openings. There was evidence in June, 1937 (one year after the first operation), that the leak was becoming re-established.

An important observation made at operation was that the brachial artery was greatly dilated, and measured approximately 2 to 2.5 cm. in diameter. Operative dissections exposed it from the bifurcation of the interosseous artery to within 6 to 8 cm. of the axilla, and it was dilated throughout this distance. The wall of the artery was thought to be moderately thinned.

<div style="text-align:center">DISCUSSION</div>

The evidence we have presented indicates that an arteriovenous fistula is associated, in the main, with the following changes in the circulation: an increase in the output of the heart; an increase in the total blood volume; an increase in the pressure and oxygen content of the venous blood near the fistula; no change in the general venous pressure in the presence of a competent heart; an increase in the heart rate; an increase in the volume of the extremity containing the fistula; an increase in the speed of blood flow in the affected part; a marked decrease of the diastolic blood pressure near the fistula; and a slight decrease of the diastolic blood pressure generally.

During the few months after operation the cardiac output and the blood volume fell. Later the blood volume again became elevated, but the output of the heart remained normal. This seems to indicate that these two functions were not controlled by the same factors in this patient.

Some authors have believed that the flow through the remainder of the body was decreased because of the fistulous leak. Our evidence favors the conception that the flow of blood through the rest of the body is normal, and that the output of the heart is increased by the fistula.

Work Done by the Heart.—From the foregoing observations it is possible to arrive at an approximate calculation of the work of the heart, and to estimate the increase in work caused by the fistula. No available formula is an exact expression of heart work. The simplest formula is the product of the weight of blood pumped per minute and the mean pressure against which it is ejected. According to this simplified formula, the work of the left ventricle, only, is taken into account (since the pressure in the pulmonary artery cannot be measured), and the so-called "velocity factor" is not taken into consideration.*

By this formula:

Work = cardiac output × B.P. (mean)

fistula open – 6.4 kg. m./min. (384 kg. m./hr.)

fistula closed – 5.2 kg. m./min. (312 kg. m./hr.)

Thus the heart does 23 per cent more work with the fistula open than with it closed.

If a more elaborate formula is used, which takes into account the "velocity factor" (such as the one devised by Evans[33]), several assumptions must be made. Using this more complex formula, the calculated work is 28 per cent greater with the fistula open than when it is closed. This increased work performed by the heart is a constant burden, is present continuously even at rest, and is comparable to the burden of hyperthyroidism, and not to an intermittent burden such as exercise. The increased work, if long enough continued, may lead to cardiac hypertrophy and to congestive heart failure.

SUMMARY

Observations on the circulation of a 19-year-old boy with an arteriovenous fistula in his forearm are presented. These demonstrated an increase in the cardiac output and the blood volume, an increase in the oxygen content of venous blood near the fistula, a rapid circulation time in the arm containing the fistula, a normal circulation time in the normal arm, and an increase in the volume of the arm containing the fistula. Data concerning the amount of blood flowing through the fistula are presented and discussed. The work of the heart was calculated and was found to be increased about 25 per cent by the fistula.

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*According to Evans,[33] the velocity factor is negligible for normal cardiac outputs at rest; it becomes more important with large outputs, but even at 21 liters per minute it represents only 9.5 per cent of the total heart work.

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FUSION BEATS AND THEIR RELATION TO THE SYNDROME OF SHORT P-R INTERVAL ASSOCIATED WITH A PROLONGED QRS COMPLEX

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IN 1911, Lewis[1] produced, experimentally, a type of electrocardiographic complex resulting from double stimulation of the ventricular muscle. These peculiar wave forms he called "transitional complexes"; more recently they have become known as "combination complexes," "parasystoles," or "fusion beats." The last term is simple, and seems to describe the phenomenon adequately. It will therefore be used in this paper.

Instances of this type of complex have been reported in human beings,[2] and Lewis' experimental work has been repeated.[3] The usual form of double stimulation arises when a ventricular pacemaker interferes with the normal sinus rhythm. This may be a regularly recurring ventricular impulse which gives rise to a regularly recurring parasystolic rhythm, as suggested by Rothberger and Winterberg[4] and illustrated by Hill and Cameron,[5] or may be simply random ventricular extrasystoles which by chance happen to fall into the limited period between the P wave and the onset of the QRS deflection during which double stimulation of the ventricles is possible.

This paper presents the experimental production of fusion beats by a more refined method than has heretofore been reported; this method permits accurate study of the variations in wave form of fusion beats. Clinical instances are also reported.

EXPERIMENTAL

In a previous paper,[6] the technique of using an amplified auricular impulse to stimulate the ventricles was described. By the introduction of a time delay system into this circuit it was possible to study the effect on ventricular response of minute, but accurately controlled, delays between the auricular impulse and ventricular stimulation.

An apparatus† was devised which produced a variable delay of electrical impulses from 0.002 second to 0.85 second. This delay was accomplished by electrical methods, and was constant under any given set of conditions. It was possible also to control the duration and voltage of the output from the device. The circuit cleared so rapidly that

rhythmic impulses many times faster than the most rapid mammalian heart rates could be handled easily. In this manner, each auricular impulse was passed into the delay circuit, and a stimulating current of any desired duration and intensity was delivered from the output of the circuit at any predetermined instant between 0.002 and 0.85 second. By the use of a cathode-ray oscilloscope, these impulses could be studied visually as the experiments were in progress.

In cats and dogs, under nembutal anesthesia, the sternum was removed to expose the heart, and the incised pericardium was sutured to the exposed rib margins to form a cradle for the heart. An automatic positive pressure respirator was used to maintain respirations after the chest was opened. The current of excitation produced by the right auricle was picked up by small, riding, silver electrodes and carried to the amplifier. The output of the amplifier was connected to a cathode-ray oscilloscope and also to the input of the time delay circuit (Fig. 1). The output of the time delay circuit was then utilized to stimulate the right
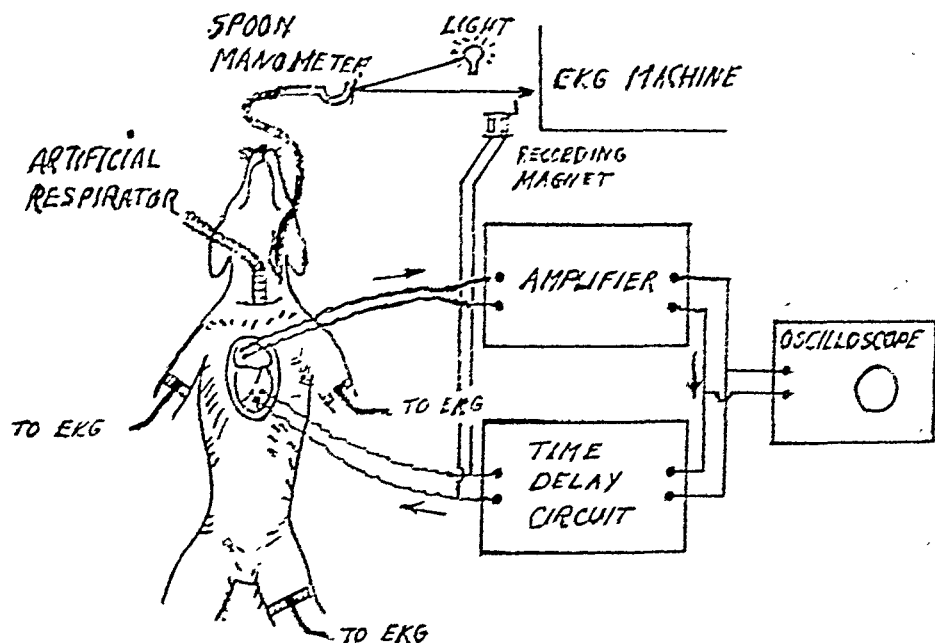
Fig. 1.—Diagram showing set-up of apparatus.

or the left ventricle by electrodes imbedded in the muscle or riding on the epicardial surface. This output current also activated a recording magnet which signaled the time and duration of the stimulus applied to the heart. The delay in the magnetic recording system was ascertained and found to be so small (less than 0.001 second) that it could be disregarded. The output voltage was adjusted to a value slightly above the threshold value for the ventricular muscle.

RESULTS

By varying the time delay it was possible to introduce a stimulating shock to the ventricles at any desired time in each cardiac cycle. Fig. 2 shows single beats selected from numerous tracings taken on the same animal and arranged in order with an increasing delay of the auricular

stimulus. There is a period of approximately 0.06 second between the introduction of the stimulating current (as represented by the down-stroke in the solid line below the tracings) and the beginning of the ventricular QRS. This delay was produced, evidently, at the epicardium, for the electrodes in this case were riding on the surface of the heart. When the stimulating electrodes were buried in the ventricular muscle, this delay disappeared. One can see, by inspection of the records, that the QRS and T complexes gradually progress from a purely extra-systolic configuration to normal. The QRS time gradually decreases, and, as this occurs, the negativity of the T waves and the voltage of the QRS complexes decrease.
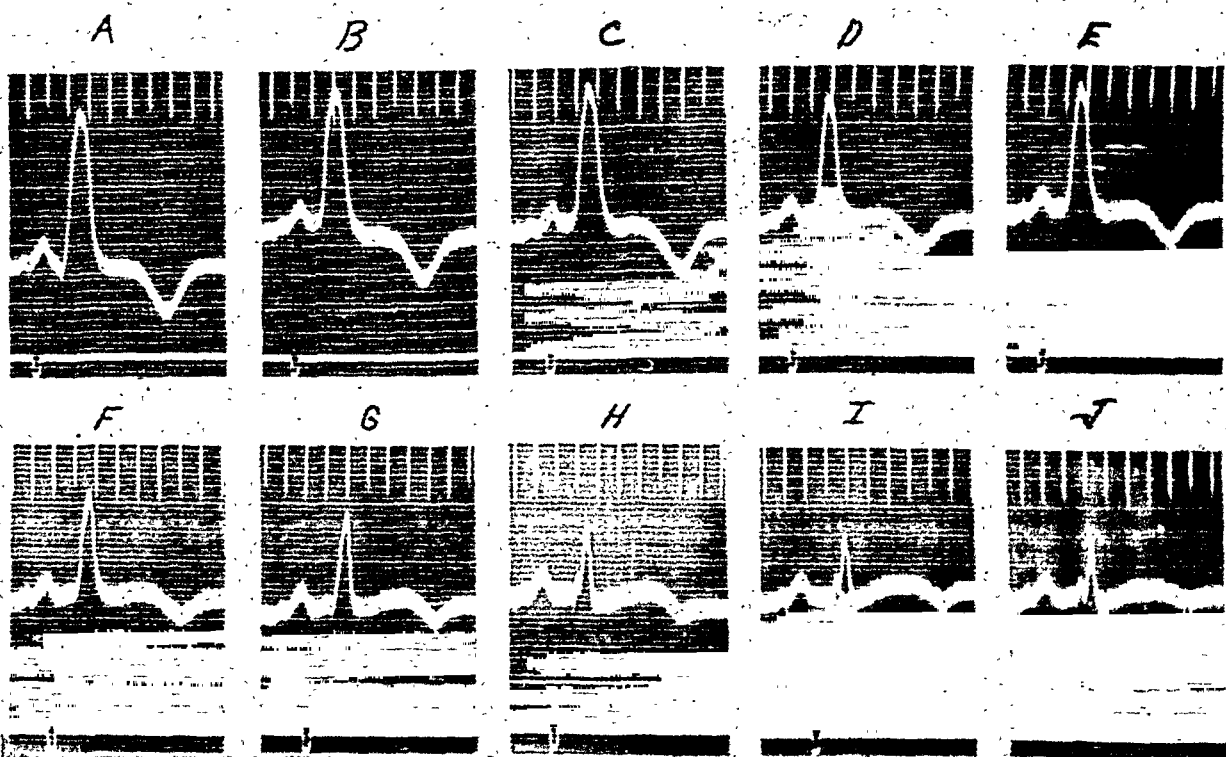
Fig. 2.—Selected complexes from the same animal, with varying degrees of delay between the beginning of the P wave and the onset of the QRS deflection arranged in order of increasing delay. The downstroke of the solid line below each tracing represents the time and duration of the ventricular stimulus. Time markers in 0.04 second. A to C, inclusive, represent extrasystolic beats, D, to H, inclusive, are fusion beats, and I and J are normal complexes.

Careful measurements of many tracings by a projection method (magnification x10) revealed that the maximum time during which fusion occurred in the dog ventricle (i.e., the time during which the ventricles can be stimulated by two or more foci) was approximately 0.035 second, although it varied slightly from animal to animal and de-pended upon the location of the stimulating electrodes. It was found that the P-T interval (time from the beginning of the P wave to the end of the QRS) remained constant.

Similar tracings are seen occasionally in man, and Fig. 3 shows such fusion beats. In this case there appears to be an idioventricular rhythm

at every second beat at, or just following, the P wave. This is probably not a true case of interference dissociation, as recorded by Hill and Cameron,[5] but records of sufficient length for complete study were not available.
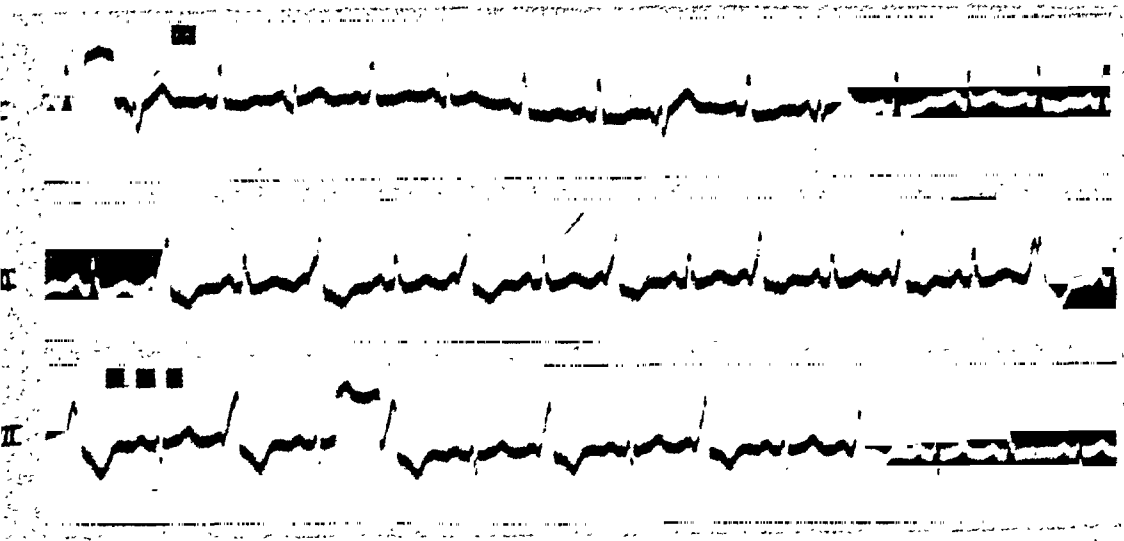
Fig. 3.—Standard leads of an electrocardiogram from a patient with numerous ventricular extrasystoles, many of which result in fusion.

DISCUSSION

From the above data it can be seen that the ventricle can be stimulated by the normal conduction system and by a second ventricular stimulus only during the short period (approximately 0.035 second in the dog ventricle) prior to the time the normal complex would ordinarily appear. This period closely approaches, but never quite attains, the duration of the normal QRS complex, which was 0.37 second in the case illustrated in Fig. 2.

This time relationship is interesting, and probably has a bearing on the relation of the QRS to activation and contraction of ventricular muscle. At the moment there is insufficient evidence at hand, but it would tend to support the supposition that the QRS time represents the period during which there is an electrical effect of excitation or activation of individual muscle cells, and does not represent the spread of the conduction wave over the bundle of His and the Purkinje network.

Fig. 4 shows superimposed drawings of actual complexes. The time from P to R is the normal P-R interval, and the time from P to R' represents the shortest P-R interval which will produce fusion. The time from R to R' thus represents the time during which fusion may occur in the ventricle of the dog. It may also be noted that the time between the beginning of P and the end of S (the P-T interval) is constant for all beats.

From these data we can say that the period of fusion is roughly represented by the duration of the QRS complex. Translating this to the

human heart would mean that, with a normal P-R interval of 0.16 second and a QRS time of 0.08 second, fusion could occur slightly less than 0.08 second before the onset of the normal QRS, and would produce a P-R interval of 0.08+ second. This is exactly what occurs in the syndrome of short P-R interval associated with wide QRS complexes. In both the experimental work and in man, the P-T interval of normal and abnormal complexes remains relatively constant.
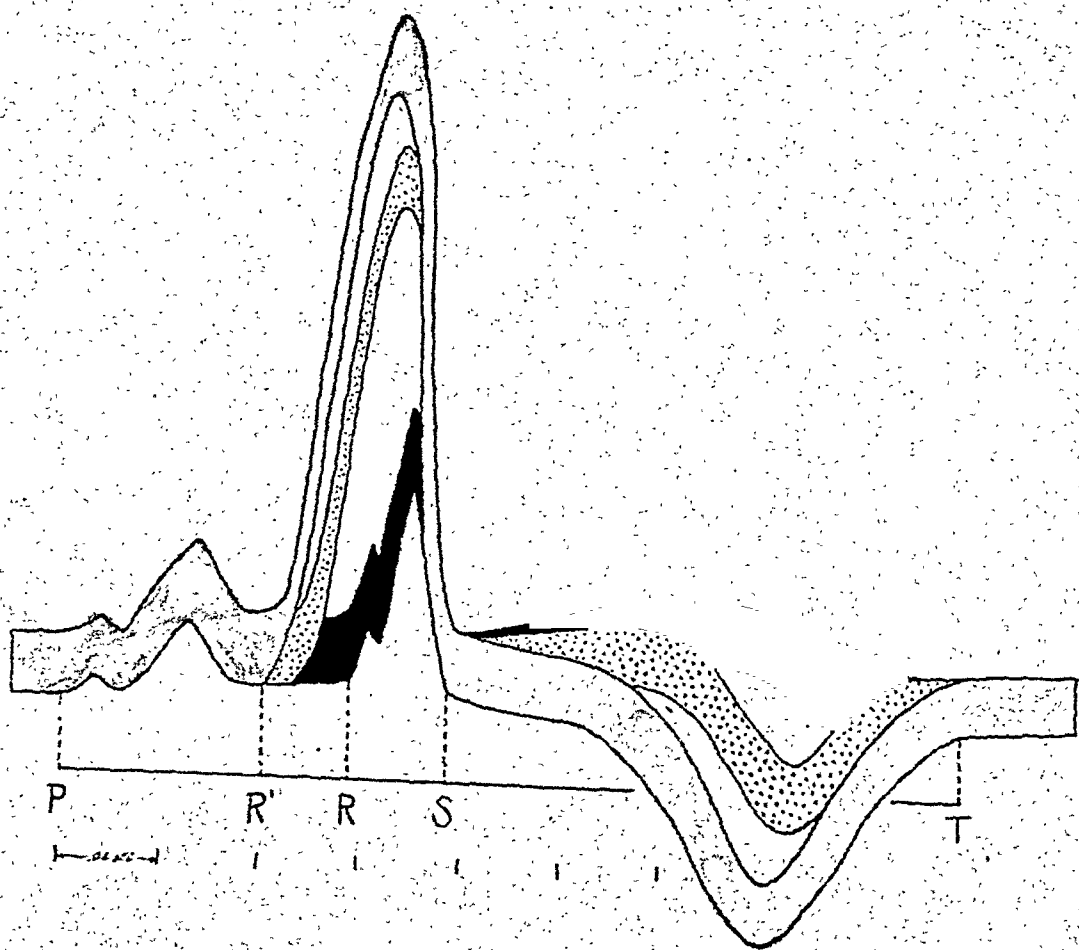
Fig. 4.—Superimposed magnified complexes from the electrocardiogram of a dog. P-R' represents the shortest P-R interval which will result in fusion. R'-R represents the time during which fusion may occur. The black complex is the normal, the gray is a purely extrasystolic form, and the stippled complex represents an intermediate fusion beat. The P-T interval (from P to S) remains constant.

It seems entirely logical, then, to assume that the abnormal complexes of this syndrome are the result of fusion, and that the type of complex depends upon the degree of fusion which exists in any individual case. Fusion beats differ in no way from those which occur in the short P-R syndrome.

Hunter, Papp, and Parkinson[7] have asserted that any hypothesis should explain (1) the difference in the shape of the P wave before normal and short P-R syndrome complexes, (2) the peculiar shape of the ventricular complexes as compared with that of ordinary bundle branch block, and (3) the gradual change of P and QRS from the

short P-R syndrome to normal (after atropine) and the appearance of intermediate complexes.

The first of these criteria has been studied carefully by Wolferth and Wood,[8] who, after examining all available reports, were unable to substantiate the statement that a change occurs in the P waves. They found "the contour of the P waves in these cases is remarkably constant when the ventricular complexes change their shape."

The second and third criteria can be explained by the experimental work recorded in this paper. The bizarre QRS complexes are probably the result of ventricular fusion, which would be expected to yield an abnormal complex, but not necessarily one similar to bundle branch block. The gradual change of the QRS from abnormal to normal which occurs in man is easy to understand if we assume that various degrees of fusion are produced as the complexes change from the abnormal to the normal form. This change may be due to an increasing conductivity of the normal pathway and a decreasing conductivity of an accessory pathway. The tracings from human beings are similar to those obtained by experimentally varying the degree of ventricular fusion (Fig. 2).

The simplest and best explanation of this syndrome thus would seem to be the assumption that there is an accessory conducting pathway[9] from the auricles to the ventricles which has a slightly faster rate of conduction than the normal conduction system of the heart. Such a path was described originally by Kent,[10] and more recently by Glomset and Glomset,[11] who noted frequent connections between the auricles and ventricles in mammalian and human hearts.

Fusion beats are probably more common than is generally recognized. Many of our routine tracings with numerous extrasystoles will show an occasional fusion beat. Of more importance clinically are the frequent fusion beats (Fig. 3) which give the impression of multiple foci premature·ventricular contractions, but which actually originate from a single focus.

Since the completion of this paper, two articles of special interest have appeared. The first is that of Fox, Travell, and Molofsky,[12] who studied the action of digitalis, atropine, and other drugs in a case of typical short P-R syndrome. They found that atropine sulfate always shortened the QRS time, and digitalis lengthened the QRS time. These effects were attributed to vagal action. Their tracings are similar to the experimental results reported above. Any factor increasing the P-R interval will allow less fusion, and, consequently, prolongation of the QRS complex will result, and the character of the complex will approach that of an extrasystolic beat. Conversely, any shortening of the P-R interval will throw the normal and abnormal stimuli closer together, decreasing the degree of fusion, and will produce a decreasing QRS time and the complex will approach the normal type.

The second paper of interest contains the long-awaited confirmation of accessory pathways in human beings with this syndrome. Wood, Wolferth, and Geckeler[12] demonstrated small muscle bundles running directly

from the right auricle to the right ventricle in the heart of a patient who had this syndrome and died suddenly during an attack of paroxysmal tachycardia.

SUMMARY

Fusion ventricular complexes were produced in animals by a method which allows accurate spacing of stimuli over short time intervals in successive cardiac cycles. The time during which fusion occurs was found to approach closely, but not quite equal, the time of the normal QRS complex.

The clinical aspects of fusion beats were mentioned, and their relation to the syndrome of short P-R interval with wide QRS complexes was indicated.

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ON THE APICAL SOUNDS AND MURMURS
IN AORTIC REGURGITATION

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EXACT knowledge and proper evaluation of the sounds and murmurs at the apex of the heart in aortic regurgitation are of great practical importance, for, often, an opinion as to the cause of the disease is based upon them.

There is no need to discuss the fact that murmurs arising at the beginning of the aorta are partly transmitted to the apex. This is particularly true of the soft, blowing, diastolic murmur caused by aortic regurgitation, but may also be true of the systolic murmur which is so often heard at the base of the heart when there are lesions of the aorta. A different type of systolic murmur may be heard at the apex when the mitral valve is insufficient, either because of marked dilatation of the left ventricle (functional insufficiency), or because of sclerosis of the valvular leaflets (anatomic insufficiency). The most important phase of auscultation, however, is diastole, for a murmur heard in this phase would lead to the diagnosis of mitral stenosis. Ever since nearly a century ago it has been recognized that diastolic murmurs at the apex in aortic regurgitation may have a functional origin. Therefore, whenever a diastolic murmur is heard at the apex. it is essential to know whether it is caused by mitral stenosis. or is of the type and nature described by Austin Flint and attributed to a functional mechanism.

BRIEF REVIEW OF THE LITERATURE

Clinical studies on apical murmurs in aortic insufficiency deal mainly with the Austin Flint murmur. It will be useful to report the words used by different authors in the description of this murmur, for no graphic study has been undertaken up to this time. In the original work of Austin Flint[1] the murmur is reported as a "presystolic blubbering murmur" heard at the cardiac apex of patients with aortic regurgitation due to syphilitic and arteriosclerotic heart disease. Laubry and Pezzi[2] describe the murmur as either a "diastolic rumble" or a "presystolic rumble." In a well-known work, White[3] says that the Austin Flint murmur has "exactly the same characteristics as the diastolic murmur of organic rheumatic mitral stenosis." Wiggers[4] describes it as a "mid-diastolic or presystolic murmur heard over the apex or mitral areas of the chest." Gouley[5] maintains that it is "a presystolic rumble which practically merges with the first sound and is limited to a small area at the apex."

The term "blubbering murmur" employed by Austin Flint probably corresponds to that of "rumble" later used by different authors in describing the diastolic murmur of mitral stenosis, and points to a *prolonged murmur*. The terms *diastolic* and *presystolic* cannot be used indiscriminately with the same meaning. When the heart rate of patients with mitral stenosis is slow, it is perfectly possible to hear either a diastolic or a presystolic murmur, or both. The diastolic murmur may be described as a "rumble;" the presystolic murmur, on the contrary, is a *short murmur* immediately preceding the first sound and merging with it. For this reason, if we accept the term "blubbering murmur" as describing a "rumble," we must admit that the murmur described by Austin Flint was a *real diastolic murmur,* and we can justify the expression used by White, as well as the more comprehensive meaning attributed by him to the murmur.[3] On the contrary, the expression *presystolic* should not be used unless we admit that the murmur is a short one, with no "blubbering" or "rumbling" character.

The mechanism by which the Austin Flint murmur is produced has been differently explained.

Flint thought that the apical murmur was due to *a functional stenosis of the mitral valve.*[1] He explained the stenosis by assuming that, when the blood stream entered the left ventricle from the aorta, it pushed the anterior leaflet of the mitral valve upwards and backwards. The blood entering the same ventricle from the left auricle would meet, therefore, with an obstacle, comparable to that caused by mild mitral stenosis. This conception was accepted, with some modifications, by Guiteras,[6] Grocco,[7] and Vaquez.[8] They thought that the anterior leaflet of the mitral valve, pushed by two different streams of blood, would vibrate, thereby causing a diastolic murmur. De Renzi[9] and Potain[10] attributed the murmur to whirlpools caused by the meeting of the two streams of blood, one entering the left ventricle through the insufficient aortic valve, and the other through the normally open mitral valve.

A different explanation was offered later by White.[3] He thought that the murmur was better explained by admitting *a relative narrowness of the normal mitral orifice in comparison with the dilated left ventricular cavity.* The blood rushing from the auricle into the ventricle would create whirlpools in the ventricular cavity and, therefore, a murmur. This murmur should not be thought of as peculiar to aortic regurgitation, but would be found in any case of ventricular dilatation, such as that caused by chronic adhesive pericarditis, or cardiac failure in cases of rheumatic or hypertensive heart disease. As a matter of fact, a rumbling diastolic murmur was described in adhesive pericarditis by Flint,[1] and Osler and Hirschfelder;[11] with dilatation of the heart in children by Fisher;[12] in young people by Bland, Jones, and White;[13] and in adults by Wood and White,[14] Weinstein and Lev,[15] and Robinow and Harper.[16]

A quite different hypothesis was advanced by Pezzi[17] and Laubry and Pezzi.[2] They do not agree that the diastolic rumble of mitral stenosis and the Flint murmur are identical, and attribute the latter to *a special kind of gallop rhythm.* The successive vibrations of the ventricular wall due to the different streams of blood entering it, and the echo of the aortic diastolic murmur would give to the ear an impression different from that of the more common gallop rhythms. Clinical considerations, pathologic studies, and graphic records were presented in support of this theory.

Interest in the Flint murmur was more recently awakened by Gouley,[5] who described a characteristic deformity of the right aortic leaflet which might divert the regurgitating blood toward the lower portion of the anterior mitral curtain. Mention should be made also of some important contributions on the hemodynamics of aortic insufficiency. The studies of Wiggers and his co-workers[4, 18-20] have shown that the regurgitation is predominant in the initial period of diastole, before the opening of the A-V valves (80 per cent in large leaks), and that ventricular filling from the auricle is not hindered, but rather increased, after the mitral valve opens.

Routine phonocardiograms show that the soft diastolic murmur which is typical of aortic insufficiency starts immediately after the second sound, and gradually decreases, so that a large part of diastole shows no evidence of regurgitation. This fact, which coincides with the accepted clinical evidence, should be kept in mind, for it confirms the conclusions reached by Wiggers and his co-workers.

TECHNIQUE AND MATERIAL

The study was carried out on twenty-seven patients in various hospitals of Greater Boston.[*] Fifteen of them were white and twelve were Negroes.

Special care was used to exclude any case in which rheumatic heart disease could be suspected. Fourteen of the patients had syphilitic heart disease, six had fibrosis of the heart valves due to atherosclerosis, and five had both syphilitic and arteriosclerotic heart disease. Two patients were included, in spite of an early diagnosis of rheumatic heart disease, because the diagnosis was not confirmed later, and also because the description of a typical diastolic rumble was thought particularly interesting. All of the patients had aortic regurgitation, as shown by clinical evidence and by records taken at the base of the heart. In addition to these cases, many others were studied, in which the clinical diagnosis was syphilitic heart disease with Austin Flint murmur, but the phonocardiogram showed typical evidence of mitral stenosis.

Our records were taken with a Stetho-cardiette (Sanborn). The following tracings were recorded: (1) A routine electrocardiogram, coupled with a routine phonocardiogram.[†] (2) Lead I of the electro-

cardiogram, and the apex phonocardiogram by employing the stethoscopic microphone.[21, 22]   (3) The same record, but using a logarithmic microphone.[21, 22]   (4) Apex sounds and apex beat.   These were recorded in accordance with the technique described by Rappaport and Sprague.[22]   (5) Various other records, such as the phlebogram, arteriogram, and pneumocardiogram.[23]

These records permitted transcription of the heart murmurs over the apex in two different ways: first, *as they are presented to the ear* by a common stethoscope (stethoscopic microphone), and, second, *as they are heard* in the ordinary stethoscopic examination of the patient (logarithmic microphone).   Presystolic vibrations were divided into two classes.   If a single or double, slow vibration, lasting only as long as the auricular contraction, was present, it was classified as an *auricular sound;* the existence of this sound excludes any anatomic or func-
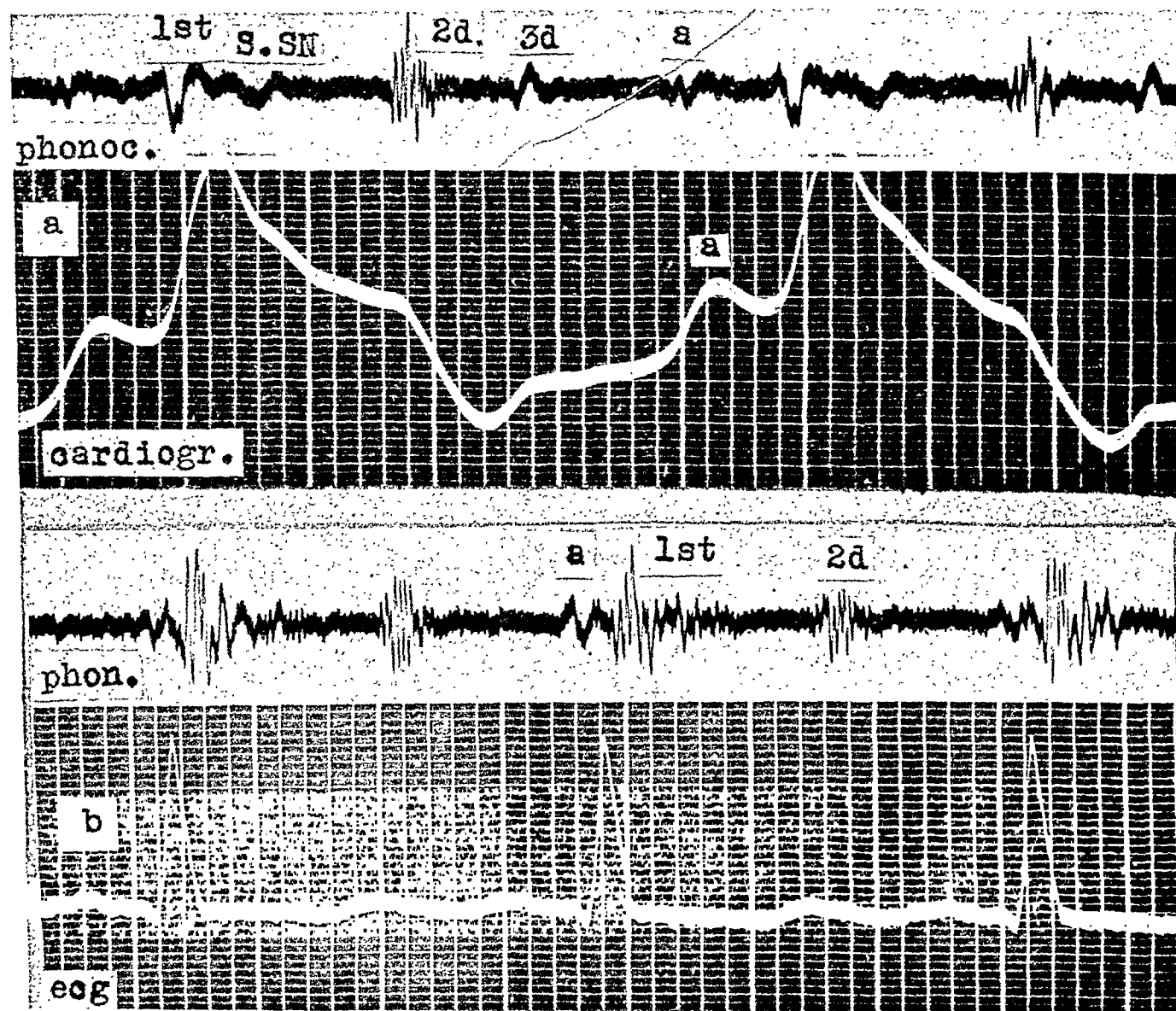
Fig. 1.—Hypertensive heart disease; myocardial fibrosis; mitral and aortic insufficiency. A diastolic rumble was heard in Case *a* at the apex, a presystolic sound in Case *b.*

a, R.H.—Apex phonocardiogram and cardiogram (stethoscopic microphone). *b*, L.McC.—Apex phonocardiogram and cardiogram (stethoscopic microphone).

In Case *a* all diastolic sounds are louder than normal. Very high auricular wave on cardiogram. In case *b* there is a loud auricular sound. *a* = auricular sound; *1st* = first sound; *2d* = second sound; *3d* = third sound; *S. SN.* = aortic snap transmitted to apex.

tional stenosis of the mitral valve, for the sound is caused by the blood stream passing with high speed through the mitral valve and striking the ventricular wall. On the contrary, the term *presystolic murmur* was applied to vibrations present in presystole, and with the following characters: high-pitched vibrations of a low amplitude, lasting longer than the auricular contraction and gradually merging with the first sound. These only can be attributed to narrowing of the mitral orifice.
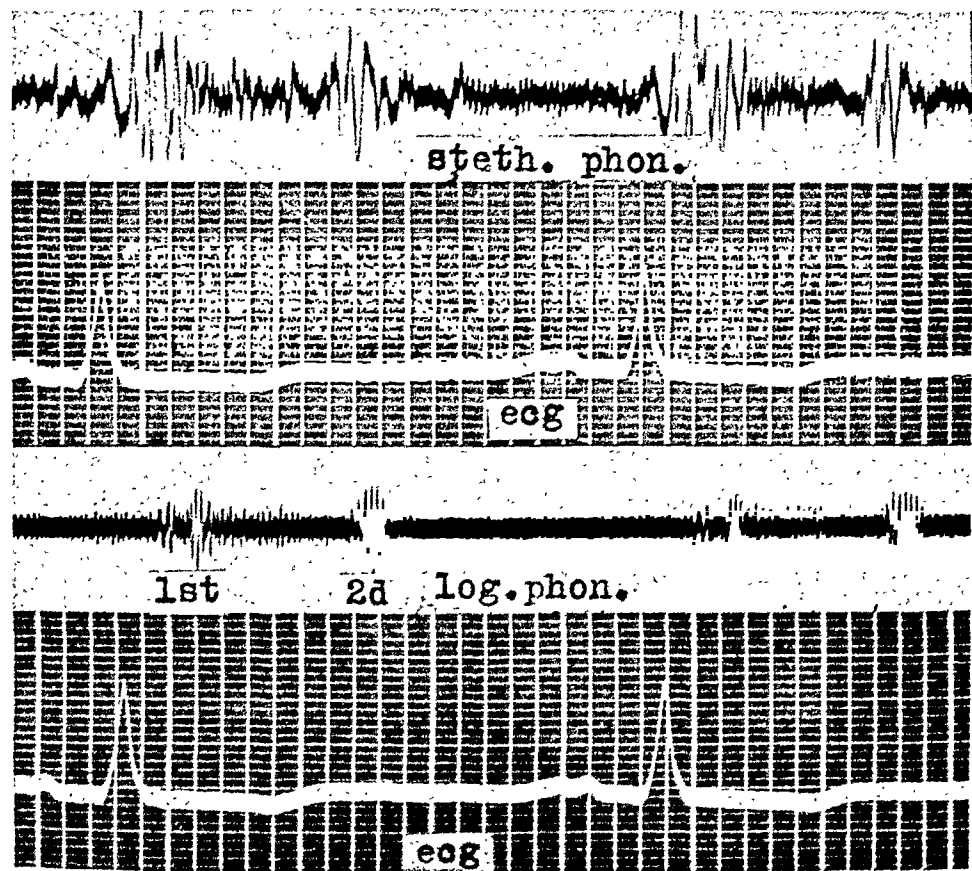
Fig. 2.—L. B.—Syphilitic heart disease: aortic regurgitation. The first sound seems preceded by a "crescendo" murmur.

a, Apex phonocardiogram with stethoscopic microphone and electrocardiogram.

b, Apex phonocardiogram with logarithmic microphone and electrocardiogram.

The logarithmic microphone does not allow a good record of the first component of the first sound. Therefore, the first sound appears as if "in crescendo." *1st* = first sound; *2d* = second sound.

RESULTS OF THE STUDY

Our cases can best be described by dividing them into three different groups.

1: In some of the cases, a very ample and slow vibration was present during presystole. This vibration was absolutely identical with the *loud auricular sound* which causes presystolic gallop rhythm. In some of the cases, the auricular sound was far enough from the first sound to be heard separately; in others, the auricular vibration merged with the first sound and gave the impression of a presystolic crescendo murmur. In some cases there was *a loud third sound of the heart, followed*

by an auricular sound (Fig. 1).   The existence of two additional sounds during diastole (third sound plus auricular sound) *may give the impression of a diastolic rumble.*

2.. In a second group of cases, tracings recorded with the logarithmic microphone showed that the first sound started with a series of small vibrations, followed by much larger vibrations (Figs. 2 and 3).   At first glance the phonocardiogram simulated that of a presystolic murmur.   However, comparison with a tracing taken with a stethoscopic microphone and with the simultaneously recorded electrocardiogram proved that *the "crescendo" murmur was really a distorted first sound and occurred in systole.*   In the case shown in Fig. 2, competent ex-
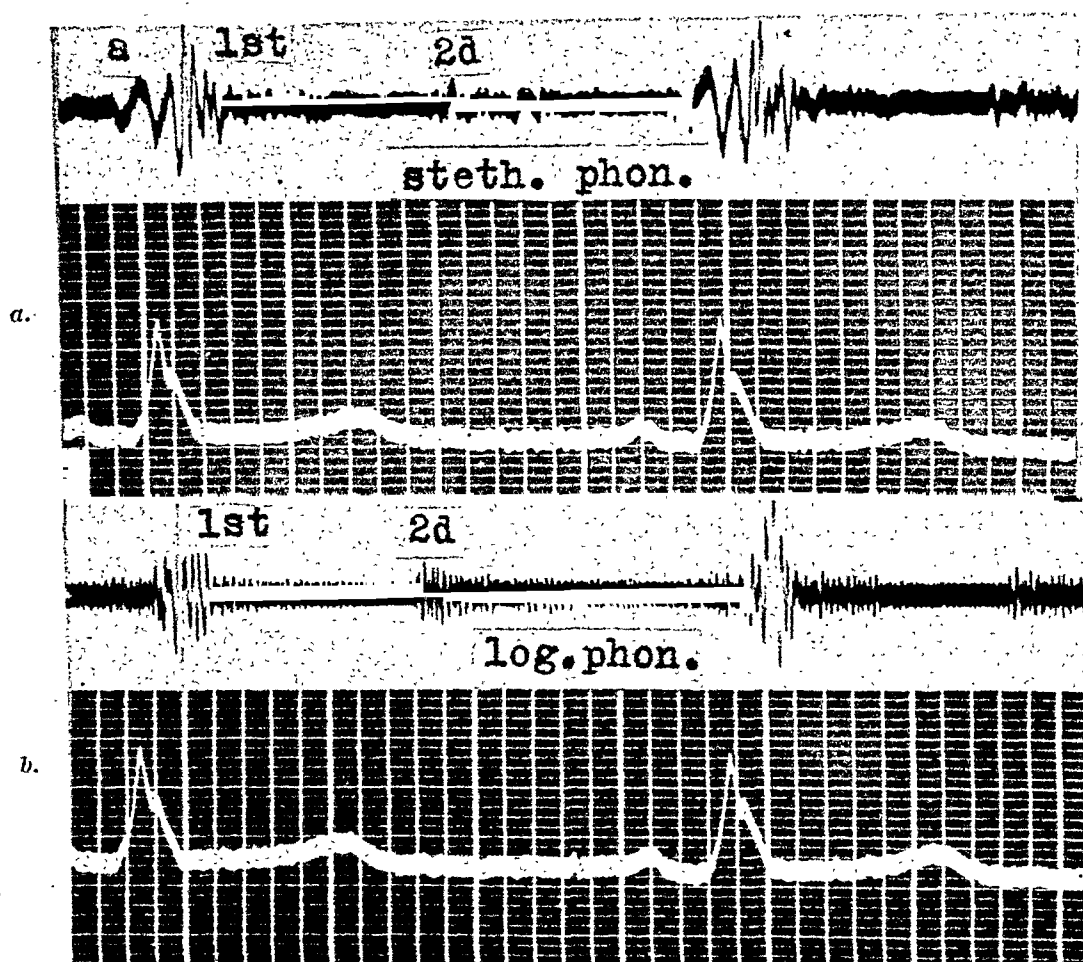
Fig. 3.—H. T.—Syphilitic heart disease; aortic regurgitation.   Diastolic rumble and presystolic murmur at apex.

a, Apex phonocardiogram with stethoscopic microphone, and electrocardiogram.

b, Apex phonocardiogram with logarithmic microphone, and electrocardiogram.

The stethoscopic microphone records the auricular sound.   The logarithmic microphone shows some tiny vibrations in diastole which are transmitted from the base, and some in presystole, probably due to the auricle.   However, the most apparent fact is the crescendo type of the first sound, due to the small amplitude of the vibrations of the first component through the logarithmic microphone.   *a* = auricular sound; *1st* = first sound; *2d* = second sound.

aminers had admitted the existence of an Austin Flint murmur.   The erroneous impression is due to the fact that some early vibrations of the first sound are low pitched, and are heard only as a gradually increasing murmur,

3. In a third group of cases *the first sound appeared to be split in two.* In some of them there was either a normal or a prolonged duration of the sound, but the two larger oscillations which are often present within the sound had a tremendous intensity (Fig. 4, *a*). In others, a series of vibrations which prolonged the first sound during systole simulated duplication of the sound (Figs. 4, *b*, 5, *a* and *b*). The type of the vibrations, the fact that they occurred in the ejection phase, and their intensity at the base of the heart showed that they were caused by eddies formed by the blood stream entering the aorta.
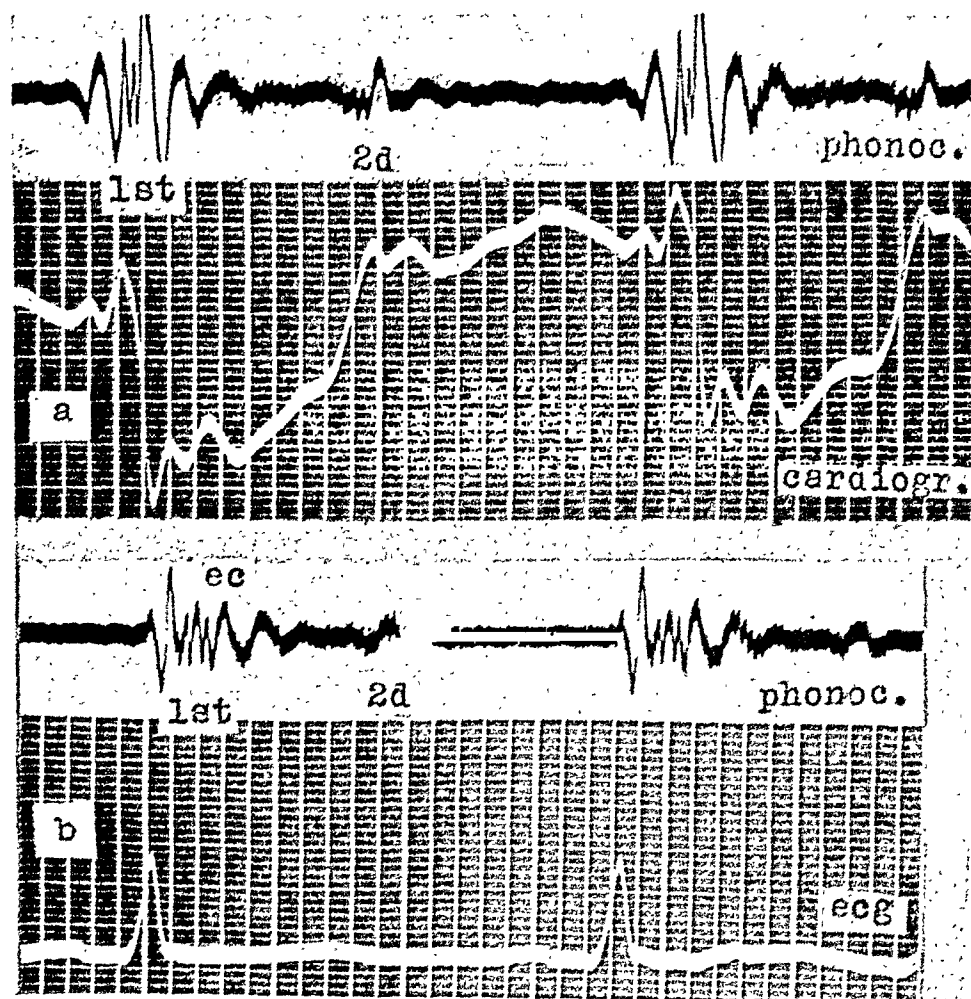
Fig. 4.—Two cases of syphilitic heart disease with aortic regurgitation. The first sound was heard as split.

a, A.B.—Apex phonocardiogram and cardiogram. The first and third components of the first sound are very loud.

b, N.D.—Apex phonocardiogram, and electrocardiogram. The first sound has a very loud first component. The ejection of the blood is accompanied by loud and prolonged vibrations. *1st* = first sound; *2d* = second sound; *ec* = ejection component.

In only one case, in which the patient had a tremendously dilated left ventricle, were low-pitched diastolic vibrations recorded. Their functional nature was shown by a very loud auricular gallop (Fig. 6).
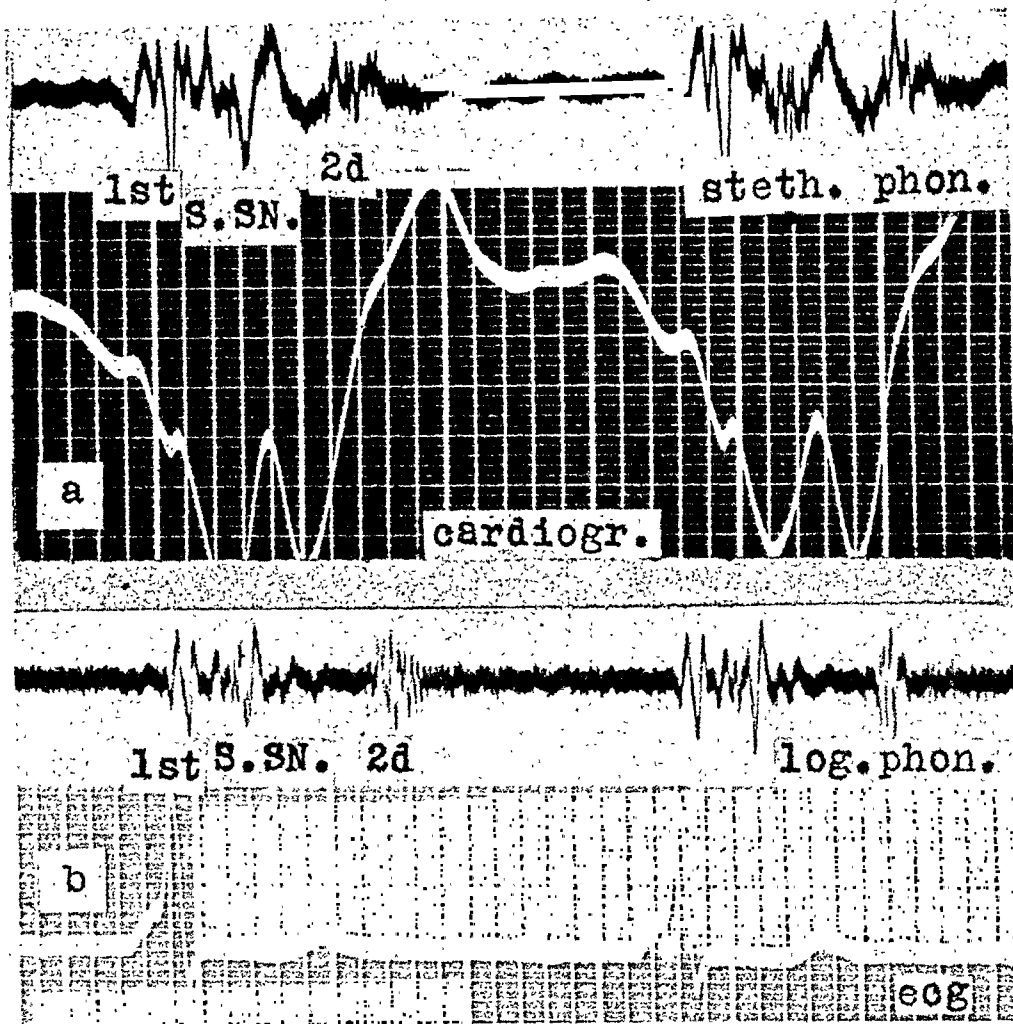
Fig. 5.—Two cases of syphilitic heart disease with hypertension and aortic regurgitation. The first sound gave the impression of being split in two.

a, A.B.—Apex phonocardiogram (stethoscopic) and cardiogram. Very high auricular wave; loud snap at the beginning of the first sound; ample vibrations occur during nearly all of systole. A low-pitched sound due to the aorta occurs in midsystole.

b, E.V.—Phonocardiogram (logarithmic), slightly inside the apex, and electrocardiogram. After an initial loud vibration the first sound becomes lower. Then a series of very high-pitched vibrations, probably due to the aorta, appears as a second snap. *1st* = first sound; *2d* = second sound; *S. SN.* = systolic snap, transmitted from the aorta.
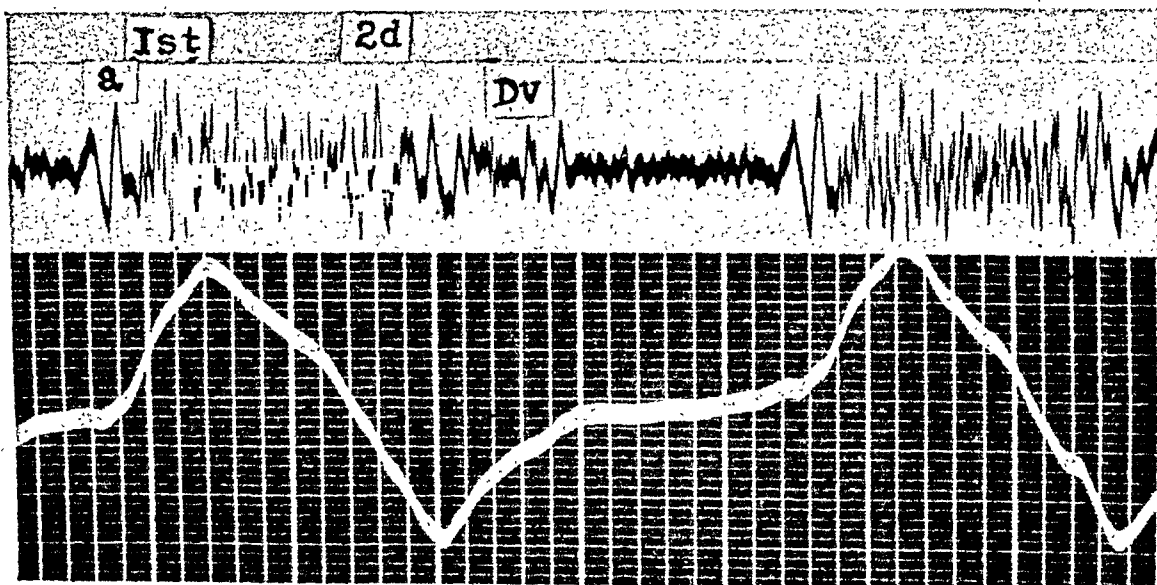
Fig. 6.—Man of 74 years with syphilitic and arteriosclerotic heart disease. Aortic regurgitation; very large left ventricle. Faint heart sounds, no diastolic murmurs heard over the apex. Phonocardiogram recorded over the apex with stethoscopic microphone. Diastolic vibration of a low-pitched type. *1st* and *2d* = first and second sound. *Dv* = diastolic vibrations.

DISCUSSION

In order to avoid likely objections, all patients with certain or even possible rheumatic heart disease were discarded. Therefore, only patients with syphilitic, hypertensive, and arteriosclerotic heart disease were studied, if aortic regurgitation was present.

This study has shown that patients with aortic regurgitation may have, at the apex, different auscultatory phenomena during diastole. These are likely due to different mechanisms.

In the cases of Group 1 there was a *diastolic rumble*, apparently because of functional changes in the ventricular wall. The rumble is due to the presence of additional sounds in diastole, mainly the third heart sound and the auricular sound. This forms a new category of gallop which I have designated previously as *train-wheel rhythm.** Adding to the diastolic sounds the echo of the aortic diastolic murmur, the ear can easily perceive a diastolic rumble. In some of the cases the extra sounds during diastole were of a very low-pitched type, and were not easily perceptible to the ear. In two of them, an Austin Flint murmur had been described, and, in one of them, the question of rheumatic heart disease was discussed for nearly a year because a diastolic rumble was heard at the apex. Later on, only a diastolic sound was heard, and the final diagnosis was that of hypertensive and arteriosclerotic heart disease.

In the cases of Group 2 the clinical impression was that they had a presystolic murmur, but this was actually an *auscultatory illusion*. As a matter of fact, there was only a distorted first sound of a "crescendo" type. There was no possibility of locating the murmur exactly, except by comparison of the phonocardiogram with the electrocardiogram. In only one of these cases did the phonocardiogram which was taken with the logarithmic microphone show a few tiny presystolic vibrations. These are due to the auricular contraction itself, and not to any supposed narrowness of the mitral valve, for the record taken with the stethoscopic microphone revealed a loud auricular sound, showing the forceful auricular contraction and the impact of the blood against the ventricular wall.

In the cases of Group 3 there was still another auscultatory phenomenon: an actually *split first sound*. This was due either to great loudness of the two valvular components of the first sound (fibrosis of both the mitral and aortic valves), or to increased intensity of the vascular component of the first sound. We have, therefore, either a separation

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*According to current classifications, the following types of gallop are recognized:
    a—Presystolic gallop rhythm, or auricular gallop.
    b—Protodiastolic gallop rhythm, or ventricular gallop.
    c—Summation gallop (both preceding sounds contribute to an extra sound in diastole).

When both the third heart sound and the auricular sound are heard because of a sufficient interval, it is improper to use the term gallop (when only three sounds are heard). Therefore, I proposed[2] for these cases the term "four-sounds rhythm" or "train-wheel rhythm." It is apparent that, when diastole is not long enough, the ear perceives the succession of extra sounds as a rumble.

of the two valvular components of the first sound, or a separation of the musculo-valvular components from the vascular component.* The ear may hear a presystolic murmur if the second acoustic element is mistaken for the first sound. In one case, the phonocardiogram showed diastolic vibrations which might have been mistaken for those of mitral stenosis. In that case, no diastolic rumble was heard because the vibrations were too low pitched. The possibility of such perception does, however, exist. Had the vibrations possessed a higher pitch, then a typical Austin Flint murmur might have been heard.

We should now discuss whether any of our patients had an Austin Flint murmur. In spite of our personal impression and of the authoritative opinion of cardiologists who affirmed it in at least four of our twenty-seven cases, it is possible that no one of them had it. After all, it should be remembered that Austin Flint, a man of very large clinical experience, described only *two* cases. This indicates that the Austin Flint murmur is a rare occurrence. Our study has shown how many factors may simulate a diastolic apical murmur. Therefore, an Austin Flint murmur should be diagnosed only after sharp criticism.

We shall conclude by saying that our study did not produce records which might be compared to the typical phonocardiographic tracings of mitral stenosis. Until they are produced, the phonocardiographic method will be an easy way to differentiate the diastolic apical rumble of mitral stenosis from the functional rumble which may be heard in aortic insufficiency.†

SUMMARY

1. A phonocardiographic study was made on twenty-seven patients with syphilitic aortic regurgitation in order to study the auscultatory phenomena at the apex.

2. Some of the patients showed one of the following acoustic phenomena:

a. The presence of additional sounds during diastole (third sound, auricular sound, or both).

b. The presence of a "crescendo" type of first sound.

c. The presence of a split first sound, due either to increased loudness of the two valvular components or to increased loudness of the vascular component.

The above-mentioned phenomena may simulate, to the ear, either a diastolic rumble or a presystolic murmur. They were easily recognized

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*These names are used here according to the descriptions of Orías and Braun-Menéndez[24] and Rappaport and Sprague.[21, 22]

†Through the courtesy of Drs. P. D. White and Eugene Stead, Jr., I have received two remarkable tracings recorded by Dr. J. C. Massee, of Atlanta. Both showed a loud diastolic murmur at the apex, with unusual characteristics (regular, musical type in the first; tremendous intensity in the second). As both patients had unusual anatomic features (everted vibrating cusps in the first, and patent foramen ovale in the other), I do not believe that they can be chosen as typical tracings. However, the rich material of the South may yield a larger phonocardiographic experience and complete our study.

on phonocardiographic tracings, so that mitral stenosis was excluded after study of the tracings.

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AN UNUSUAL EFFECT OF INTERPOLATED VENTRICULAR PREMATURE SYSTOLES

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INTERPOLATED premature systoles were first reported by Wenckebach.[1] Prolongation of the a-c interval in the jugular pulse tracing of the beat following an interpolated premature systole was first described by Mackenzie[2] and Hay,[3] and was attributed to stimulation of the A-V bundle by the premature beat, causing a delay in the passage of the subsequent sinus impulse over this bundle. Laslett[4] clearly stated that the influence of retrograde conduction from the point of origin of the extra stimulus upon the A-V bundle might account for the P-R prolongation after interpolated ventricular premature systoles. This interpretation was also advanced by Wenckebach,[5] and used by him, and later by Ashman,[6] as an argument against the theory of heart block which ascribed A-V block to a lack of responsiveness, that is, increased latency, on the part of the ventricular musculature (Erlanger,[7] Straub and Kleemann,[8] and Straub[9]). Myers and White[10] assumed that the impulse responsible for the extra beat traversed the A-V bundle and was blocked at the junction with the A-V node, the point of lowest conductivity.

The longest P-R intervals of postextrasystolic beats in the presence of interpolated ventricular premature systoles previously reported were 0.30 second (Straub[9]), 0.325 second (Ashman[6]), 0.34 second (Wenckebach and Winterberg[11]) and 0.36 second (Zeisler[12]). In all these cases the P-R intervals of the other sinus beats were normal (0.17 to 0.18 second). Ashman[6] reported a case in which the P-R interval in the postextrasystolic beat was 0.43 second as compared with a P-R interval in the other sinus beats of 0.21 second. The prolongation of the P-R above its ordinary value in the foregoing cases was, therefore, 0.115, 0.155, 0.17, 0.18, and 0.22 second, respectively.

Recently we encountered a case of interpolated ventricular premature systoles in which the effect on the P-R interval was considerably more marked, with the result that the P-R was prolonged in several instances even in the second postextrasystolic beat, a phenomenon that to our knowledge has not been described previously. The records (Figs. 1 to 3) were obtained on a 77-year-old patient with syphilitic aortitis and angina of effort.* Frequent premature systoles were noted clinically, and they oc-

curred in the absence of digitalis medication. The first record (Fig. 1) was taken to identify the premature systoles. It shows sinus rhythm with frequent premature systoles of the same ventricular origin, two of which are interpolated. In addition, intraventricular block of the common type is present. The interpolated beats occur in Leads III and CR₂. In both, the prolongation of the P-R in the postextrasystolic beats
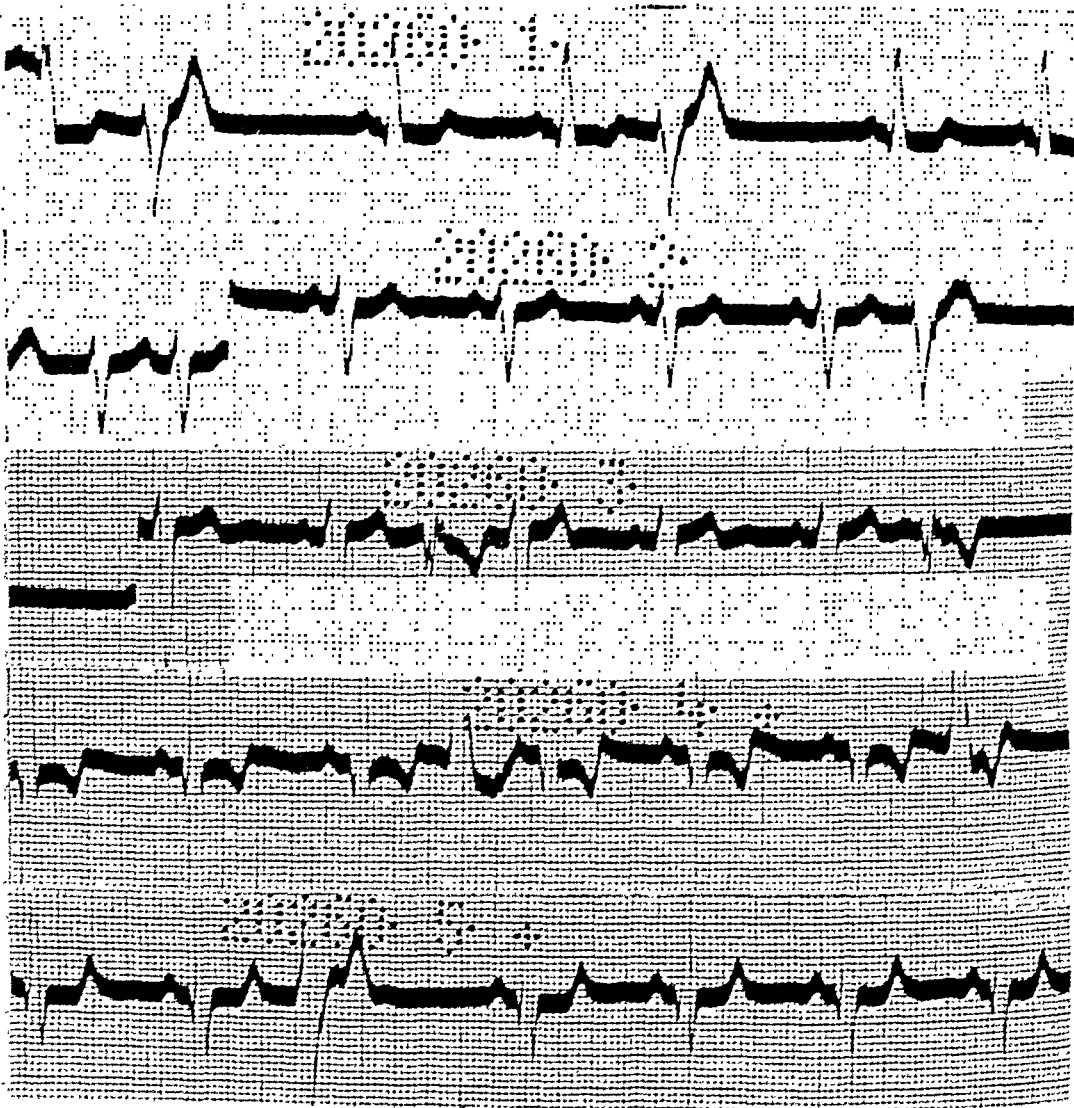
Fig. 1.—A five-lead electrocardiogram showing intraventricular block of the common type and frequent ventricular premature systoles, some of which are interpolated. Discussed in text.

is easy to discern on the following analysis: By spacing off the P waves it will be seen that the sinus P falls in the S-T-T complex of the premature beat, producing notching which is clearly visible in CR₂ but not in Lead III. Furthermore, the R-R interval of the sinus beats lengthens at the time of the premature systole, and shortens in the subsequent cycle, without accompanying changes in the P-P interval. The delay

in the occurrence of the postextrasystolic QRS-T is thus attributable to the prolongation of the P-R interval.

It was in this way that the arrhythmia at the beginning of Lead II was accounted for. The T wave with which the record starts is larger than the T waves of the sinus beats, and resembles that of the ventricular premature systole which occurs later in this lead. The ventricular complex that follows was considered to be a postextrasystolic beat with a very long P-R, following an interpolated ventricular premature systole; the P wave had occurred (off the record) on the S-T segment of the premature beat. The postextrasystolic QRS-T occurs so late that the next sinus P falls on its T wave. This can be verified by spacing back the sinus P-P interval and by comparing this T wave with that of the other sinus beats. If this interpretation is correct, the P-R of the first postextrasystolic beat is prolonged to more than 0.50 second. In order to verify this interpretation, a long record of Lead I was taken three weeks later and analyzed in detail; a total of 156 premature systole were available for the analysis. The effects on the P-R interval of the postextrasystolic beats at this time are summarized in Tables I and II, and the more significant portions of this long record are shown in Figs. 2 and 3.

Several types of premature systoles were observed. On two occasions a premature systole occurred which resembled somewhat the sinus beats in configuration and in QRS duration, but was not preceded by a premature P wave. These two beats were considered to be nodal premature systoles (cf. last premature systole of Fig. 2, A), both were interpolated, their coupling to the preceding ventricular complex was fixed (0.46 second), and they caused a slight prolongation of the postextrasystolic P-R interval (0.19 second). The other premature systoles differed strikingly from the sinus beats; they had a bizarre contour and wider QRS complexes, and were not preceded by premature P waves; they were considered to be of ventricular origin. Two varieties of these beats were encountered; the rarer type occurred only three times. In one instance shown in Fig. 2, B, a pair of ventricular premature beats occurred, the first one of the common, the second the rarer, type. The rarer type of premature systole had a shorter coupling to the preceding ventricular beat (0.44 to 0.48 second) than the more common type (0.56 to 0.70 second). The sinus node discharged impulses irregularly, so that the P-P interval preceding the preextrasystolic beats varied from 0.85 to 1 second. In addition, the P-P interval including the premature systole usually was somewhat shorter, although, on occasion, it was longer, than the preceding P-P. The P-R of the sinus beats measured 0.14 to 0.16 second after ventricular premature systoles with compensatory pauses; this value is in the range of sinus beats other than those which follow interpolated premature systoles.

Of the 152 instances of single ventricular premature systoles encountered in the long record, 90 were followed by a compensatory pause

Fig. 2.—Three portions of the long strip of Lead I obtained on the same patient three weeks after Fig. 1 was recorded. C and D are continuous, with the last two beats of C repeated at the beginning of D. A, The first premature systole is of ventricular origin and is interpolated. The sinus P wave which follows is superimposed on the top of its T wave, and the postextrasystolic P-R is slightly prolonged. The second ventricular premature systole is of A-V nodal origin; it is interpolated, and is responsible for the slight P-R prolongation of the postextrasystolic beat. The third premature systole is followed by a compensatory pause, and the following sinus P wave appears as a notch on the S-T segment. B, There are three ventricular premature systoles from two different foci. Note that the P-R of both the first and second postextrasystolic beats is prolonged after the single interpolated ventricular premature systole, the first more markedly. C and D, This segment shows clearly that the duration of the postextrasystolic P-R does not depend exclusively on the interval between the beginning of QRS of the premature systole and the sinus P wave (R-P). Thus, after the first premature systole in C and the first and second in D, the R-P is about equal in all three instances (P can be identified as a notch after QRS). However, the P-R of the postextrasystolic beat is only slightly prolonged after the first premature systole in C, is markedly prolonged after the first in D, and is infinity (not conducted) after the second premature systole in D, the following sinus P wave occurs later in D, close to the top of its T wave, than after the first premature systole in C, and D, and yet the former is not followed by a ventricular response. These variations cannot be accounted for by differences in C, and D, and yet the former is not followed nor upon the variation in nerve tone as revealed by changes in the coupling of the premature systoles to the preceding beat. Actually, the coupling and sinus rate show no significant variation during the time segments C and D were recorded. Discussed in text.
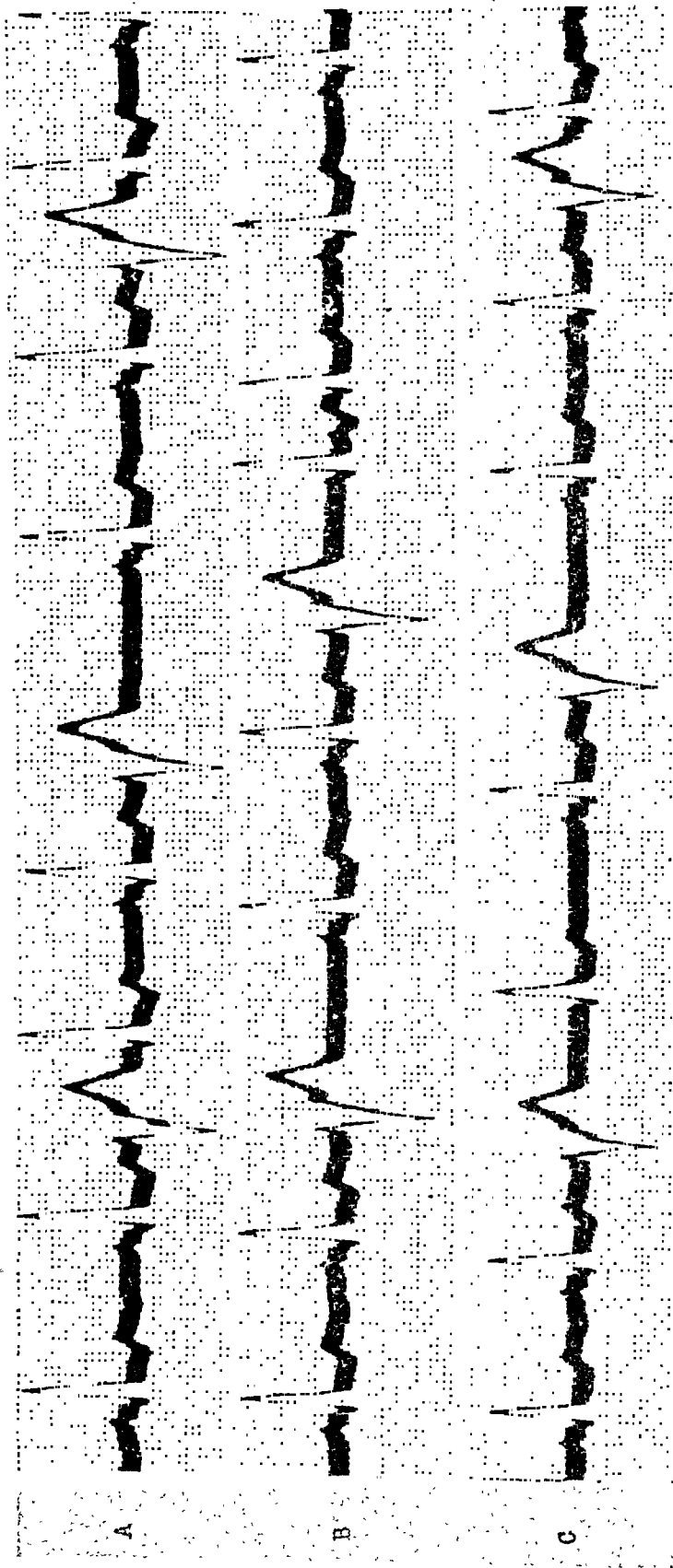
Fig. 3.—Three further portions of the long strip of Lead I obtained three weeks after Fig. 1 was recorded, to illustrate the varying effect of interpolated ventricular premature systoles on the second postextrasystolic beat. A, The first and third premature systoles are interpolated, and the second is followed by a compensatory pause. With only slight prolongation of P-R in the first postextrasystolic beat after the interpolated ventricular premature systoles, the second postextrasystolic P-R is of normal duration. B, Only the second premature systole is interpolated. With marked prolongation of the P-R in the first postextrasystolic beat after this interpolated ventricular systole, the second postextrasystolic P-R is prolonged. C, The first and third premature systoles are interpolated, and the second has a compensatory pause. After the first premature systole, the maximal postextrasystolic P-R prolongation occurred, and, as a result, the second postextrasystolic impulse is blocked. The first sinus P wave after the first premature systole gives rise to a notch on the ascending limb of its QRS, and is followed by a ventricular response after a P-R interval of 0.78 second. The second postextrasystolic P after this premature systole can be identified as a notch at the base of the descending limb of R of the first postextrasystolic beat; it is not followed by a ventricular response (the P-R interval equals infinity). With moderate prolongation of P-R in the first postextrasystolic beat after the third premature systole, the second postextrasystolic P-R is slightly prolonged. Discussed in text.

TABLE 1

THE EFFECT OF THE VENTRICULAR PREMATURE SYSTOLES ON THE P-R INTERVAL OF THE FOLLOWING SINUS BEAT, CLASSIFIED ACCORDING TO THE TIME THAT THE SINUS P OCCURRED AFTER THE QRS OF THE PREMATURE BEAT

R-P (in sec.)	.09	.10	.12	.14	.15	.16	.17	.18	.19	.20	.21	.22	.23	.24	.25	.26	.27	.28	.29	.30	.31	.34	NOT MEASURABLE
P-R (in sec.)	.18 .78	.18 .18	.38	.18 .18 .18 .72 .68	.18 .42	.18 .18 .18 .18 .18 .18 .18 .18 .18 .18 .18 .55 .53 .50 .48 .44	.18 .18 .54 .58	.18 .18 .18 .18 .18 .18 .18 .18 .18 .18 .18 .18 .18 .18 .18 .54 .49 .46 .42 .40 .38 .34 .34	.18 .18 .68 .54	.18 .18 .18 .18 .18 .18 .58 .38	.18 .18 .18 .18 .18 .70	.18 .18 .18 .52 .48 .47 .45 .37 .34 .30	.36	.18 .50 .42 .42 .40 .40 .36 .47	.18	.18 .46 .46 .42 .36 .28 .26 .26 .26 .64	.28			.33	.22	.20	35 times; 8 times ?
TOTAL NUMBER OF BEATS	21	2	1	6	2	17	4	22	4	9	6	10	1	8	1	10	1	0	0	1	1	1	43
NUMBER OF BEATS CONDUCTED (%)	.78		38			36		36				62				93							
AVERAGE P-R OF CONDUCTED BEATS IN SEC.	.596					.470						.110				.306							

TABLE II

THE EFFECT OF THE INTERPOLATED VENTRICULAR PREMATURE SYSTOLE ON THE P-R INTERVAL, OF THE SECOND SINUS BEAT FOLLOWING IT, CLASSIFIED ACCORDING TO THE TIME THAT ITS P OCCURRED AFTER THE QRS OF THE FIRST POSTEXTRASYSTOLIC BEAT

R-P (in sec.)	.10	.20	.24	.30	.32	.36	.38	.40	.42	.44	.46	.48	.50	.52	.54	.56	.58	.60	.62	.64	.66	.68	.70	.72	.74	.76
P-R (in sec.)	∞	.28	.24	.20	.20	.20	.20	.20	.19	.18	.18	.18	.18	.18	.18	.17	.17	.16	.16	.16	.16	.16	.16	.16	.16	.16
			.22		.20	.20		.19		.18	.18		.18	.17	.18	.17	.17			.16		.16		.16	.16	.16
								.19		.18	.18		.18	.17	.17	.17	.17			.16						
										.18	.18			.17	.17					.16						
										.18					.17					.16						
										.18					.17					.16						
										.18					.17											
Total number of beats	1	1	2	1	2	2	1	3	1	7	4	1	3	4	7	3	3	1	1	5	1	2	1	2	1	2

(viz., the second one in Figs. 2, *A, C,* and *D,* and 3, *A,* and *C,* and the first one in Fig. 3, *B*), and 62 were interpolated (viz., the first one in Fig. 2, *A, B, C,* and *D,* the first and third in Fig. 3, *A* and *C,* and the second in Fig. 3, *B*).

The P-R interval of the first postextrasystolic beats after the interpolated premature systoles ranged from 0.20 to 0.78 second. In order to ascertain the factors responsible for this P-R prolongation, the P-R was correlated with the R-P interval, as measured from the beginning of the QRS complex of the premature systole to the beginning of the following sinus P. In 43 instances it was not possible to identify this sinus P wave clearly, and, therefore, no measurements were made. Most of these (35) were instances with compensatory pauses, and only 8 were in interpolated beats. However, in 55 cases with compensatory pauses and in 54 with interpolated beats, these measurements could be made. In making the measurements, it was more convenient to use the summit of P than its beginning. The values given in Table I are therefore values obtained from the peak of P, less 0.06 second for R-P and plus 0.06 second for P-R. The value 0.06 second was the average duration of the upstroke of P.

Although there was a tendency for the ratio of blocked to conducted postextrasystolic sinus P waves to decrease as the R-P interval lengthened, the exceptions were striking and frequent (Table I). Thus, some P waves, which occurred up to 0.26 second after QRS of the premature systole, were not followed by a ventricular response, whereas other P waves, occurring much earlier, as early as 0.09 second after the premature QRS, were conducted (also compare the first and second premature systoles in Fig. 3, *C*). This might suggest a supernormal phase of recovery, but against this is the wide overlap shown in Table I, as well as the marked variations of P-R in conducted postextrasystolic beats. Although the shortest R-P was followed by the longest P-R, and vice versa (compare the first premature systole in Fig. 3, *A,* with the first in Fig. 3, *C*), the values between these extremes varied considerably at each R-P. For instance, at an R-P of 0.18 second, the P-R range was 0.34 to 0.54 second. Furthermore, an R-P of 0.12 second was followed by a P-R of 0.38 second, whereas an R-P of 0.19 second was followed in one instance by a P-R of 0.68 second (compare also the first premature beat of Figs. 2, *C,* with the first in Fig. 2, *D*). It is thus apparent that the interval between the interpolated premature beat and the sinus P wave was not the only factor determining the P-R interval of the postextrasystolic beat, although its influence is clearly revealed on the average values (Table I).

In attempting to account for this lack of relationship between the postextrasystolic P-R and the preceding R-P interval, an effort was made to correlate this P-R with the P-P interval as a measure of nerve tone, and with the coupling of the premature beat to the preceding

ventricular complex as a possible measure of the speed of retrograde conduction. These added measurements revealed no clear correlations. We are forced to conclude, therefore, that, although varying extracardiac nerve tone may influence the P-R duration of the first postextrasystolic beat (Wenckebach and Winterberg;[11] Zeisler[12]), the value of these P-R intervals is determined, in part, by variations in the retrograde conduction of the premature systoles. Otherwise, it would be difficult to account for the difference in the P-R to R-P relationship of the first and the second postextrasystolic beats. In the latter the correlation is clear (Table II) and in the former it is absent, and the difference appears to be due to the fact that the premature ventricular beats precede the former.

The occurrence of so many P-R intervals of 0.50 second or more after interpolated premature systoles, while the other sinus beats have a normal P-R, is unusual, and the P-R values of 0.68, 0.72, and 0.78 second are unique under these circumstances. The postextrasystolic P-R of 0.78 second is shown after the first premature systole in Fig. 3, C. In this instance the sinus P is identified by the notch near the top of the ascending limb of QRS of the premature beat. As a check on this measurement, as in all other instances, an indirect method was employed: The R-R of the sinus beats preceding the premature beat (equals 0.84 second) was subtracted from the R-R interval of the sinus beats including the premature systole (equals 1.48 second). The difference, 0.64 second, represents the lengthening of P-R over the ordinary value of P-R (equals 0.14 second), making the P-R of the postextrasystolic beat 0.78 second. The only assumption here is that there was no sinus arrhythmia at the time. In this instance this tremendous P-R prolongation makes the second sinus P after the premature systole occur near the downstroke of the first postextrasystolic QRS, and hence, since it falls in the absolute refractory period of the A-V junctional tissue and ventricles, it is blocked. This accounts for the long pause after the first postextrasystolic QRS-T. That this is so is shown by the fact that the R-R interval between the second and fourth sinus beats of Fig. 3, C, equals three sinus R-R intervals. This effect of the premature systole on the following two sinus beats is extraordinary.

The marked prolongation of the first P-R after the interpolated premature systole shortens the following R-P, and, in this way, affects the P-R of the second sinus beat after the interpolated premature systole. Besides the unusual instance of a blocked P wave, a number of instances of definite, and several of slight, P-R prolongation in the second postextrasystolic beat were encountered (cf. Table II, second premature beat of Fig. 3, B, and first premature beat of Fig. 2, B and D). As Table II shows, the P-R effect is dependent on the R-P, and is a manifestation of the influence of the absolute and relative refractory period after the first postextrasystolic beat.

SUMMARY

1. A case of interpolated ventricular premature systoles is presented in which there was unusual prolongation of the postextrasystolic P-R intervals; they attained 0.78 second in one instance, and over 0.60 second in three others.

2. The marked prolongation of the postextrasystolic P-R interval after interpolated ventricular premature systoles had a hitherto undescribed effect on the second postextrasystolic beat, namely, prolongation of its P-R and, on one occasion, dropping out of the second postextrasystolic ventricular complex.

3. Analysis showed that the P-R of the first postextrasystolic beat did not depend exclusively on the interval between the beginning of QRS of the premature systole and the next sinus P wave which occurred; some other factor was involved. Reasons are given for the view that this most likely depended upon variations in the retrograde conduction from the point of origin of the ventricular premature systole. The P-R of the second postextrasystolic beat, on the contrary, depended exclusively on the interval between its P and the beginning of the preceding QRS.

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THE RELATION OF NEUROCIRCULATORY ASTHENIA TO GRAVES' DISEASE

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INTRODUCTION

THIS rather ill-defined disorder, without a background in morbid anatomy, which has at various times been called "effort syndrome," "disordered heart action of soldiers," "autonomic imbalance," and (from its discoverer) "Da Costa's syndrome," has not obtained the dignity of a nosological entity. Because of the vagueness of its clinical outlines, both symptomatic and objective, its definition is more or less arbitrary, and, for this reason, the term syndrome seems decidedly more applicable. We believe the failure to place this syndrome into its proper category is due to the current tendency to view disease from the static rather than the dynamic viewpoint, and the failure to grasp the fact that biology[1] has its role in the interpretation of disease processes. If this view is taken, neurocirculatory asthenia presents so many features in common with the larval, or constitutional, phase of Graves' syndrome that we believe the two are identical, and it is with the exposition of this thesis that this paper is concerned. Indeed, the resemblance between the two maladies is so strong that most writers who believe in the specificity of neurocirculatory asthenia as a disease entity concern themselves with the differential diagnosis of this malady from Graves' syndrome. This concept is not new; it has been broached a number of times, especially during the last war by Barr,[2] Brooks,[3] Carrol,[4] and Grotti,[5] but on what we believe to be insufficient evidence.

In order to elucidate our thesis, we shall take up the various clinical characteristics of neurocirculatory asthenia, as currently described, and show their similarity to those of Graves' syndrome.

Symptomatology.—The conventionally described symptoms of neurocirculatory asthenia are breathlessness (especially on effort), palpitation, fatigue, dizziness, occasional precordial pain, sighing respiration, headache, dry mouth, occasional syncope, and diarrhea. Usually, there is anorexia. Sir Thomas Lewis[6] describes this attitude as "frozen with fear with wide staring eyes." Moreover, these symptoms are not by any means strictly related to war, but occur even in adolescents, especially under the influence of emotion.[7-11] This fact, coupled with others that we shall mention, effectively disposes of the notion that neurocirculatory asthenia is strictly a war disease. The similarity of

these symptoms with those of Graves' syndrome is too obvious to require discussion. In fact, they are identical with those we have often observed in patients under emotional strain, whom we have known well before the onset of the typical Graves' syndrome, and to whom the diagnosis of cardiac neurosis, psychoneurosis, or autonomic imbalance[12] was applicable. Moreover, these symptoms are observed not infrequently for varying periods after subtotal thyroidectomy for genuine Graves' syndrome, sometimes for the remainder of the patients' lives.

Physical Signs.—The characteristic physical signs of neurocirculatory asthenia[6] are tachycardia, coldness and blueness of the hands, hyperpnea or tachypnea, tremor, sweating of the palms and axillae, asthenia, and dermographia.

a. Tachycardia: This appears to be the most conspicuous and consistent sign of neurocirculatory asthenia. In the first World War, most observers, and especially Sir Thomas Lewis,[6] ascribed the tachycardia to effort, but, in the present war, it is the opinion of most British observers that the tachycardia is due not so much to effort as to emotion. Thus, Jones and Lewis[9] say that "it is not effort but the situation in which effort is required and the emotional attitude of the man toward this situation that are significant factors." They noted, for instance, that, in the carpenter shop, the patients showed no evidence of tachycardia as compared to other forms of training. Wood[7] expresses himself in a similar vein. This effect is comparable to that which one sees in the initial phase of Graves' syndrome. The point is frequently raised that the tachycardia of Graves' syndrome differs from that of neurocirculatory asthenia in that it does not tend to disappear at rest. If we compare neurocirculatory asthenia to the florid and full-fledged type of Graves' syndrome, this is more or less true, but, in the larval, or initial, phase of Graves' syndrome, we have observed repeatedly that, under conditions of emotional and physical rest, the tachycardia subsides.

b. Coldness and blueness of the hands: These signs are by no means always present in neurocirculatory asthenia: according to Wood, this sign was noted in 44.5 per cent, and its pathognomonic significance has been further minimized by the observation of Sir William Osler (quoted by Wood) that, in England, cold, blue hands are exceedingly common because of climactic conditions. Nevertheless, this sign is repeatedly used to differentiate between neurocirculatory asthenia and Graves' syndrome. That the hands are warm in Graves' syndrome because of peripheral vasodilatation[12] is well known, but this is true only in the florid types. In the larval or constitutional phase, before the basal metabolic rate has become elevated, we have noted cold hands as often as not. At best, this sign is indecisive.

c. Hyperpnea and tachypnea: These symptoms are common in emotional states with or without organic heart disease, and have little significance as diagnostic differentials.

d. Tremor: The tremor is generally believed to be coarser in neurocirculatory asthenia than in Graves' syndrome, but it is questionable whether this is sufficiently decisive to be used as a diagnostic point. In our experience, the tremor varies widely in Graves' syndrome, depending partly on the stage of the disease and partly on the emotional state of the patient. In the constitutional stage of Graves' syndrome, the tremor is more often coarse than fine, and, if absent, it can be induced or intensified by an injection of adrenalin, thus supporting the view of Cannon[14] that, under the stimulus of fear, hyperadrenalemia is induced (Goetsch test). Suggestive in this connection is the observation of Peabody, Clough, Sturgis, Wearn, and Tompkins[15] that the Goetsch test was positive in 60 per cent of their soldiers with irritability of the heart; usually there was a temporary rise in the basal metabolic rate in these cases. Boas[16] found the Goetsch test positive in 29 per cent of his cases. The cause of this difference is not clear.

e. Sweating of palms and axillae: This symptom does not differ in the slightest from that usually observed in Graves' syndrome.

f. Asthenia: It differs in no essential from that of Graves' syndrome.

g. Dermographia: This is exceedingly common in both conditions.

The close similarity between these symptoms and signs and the classical description of Darwin[17] of the expression of fear, which, as we shall see, is the dominant exciting agent of both disorders, is indeed striking. Both Crile[18] and Wood[7] stress this analogy.

Occurrence in Civilian Life.—That the occurrence of neurocirculatory asthenia is not strictly limited to wartime is obvious to every general practitioner, and, moreover, it is extremely common in civil life. Thus, White and Jones[19] noted it in 302 of 3,000 patients who had cardiac complaints; in 62 additional cases it was accompanied by organic heart disease. The reason for its prominence during wartime is undoubtedly fear. One of us[20] has already called attention to the fact that Graves' syndrome, like most psychosomatic diseases, bears a distinct relation to great crises and emotional waves, and, broadly, to the increased strain of living.

Age.—Both neurocirculatory asthenia and Graves' syndrome occur at all ages. The reason for the greater preponderance of neurocirculatory asthenia in the third and fourth decades is the circumstance that this is the military age. Both are rare in children[21] before the emotive and sensitizing faculties are fully developed.

Sex.—There is a current notion that neurocirculatory asthenia is a masculine disease because most reports are concerned with soldiers, but it is exceedingly common in women. Indeed, Craig and White[22] and Wood[7] agree that two-thirds of the cases occur in women. As

Wood expresses it, "the change of sex and the lack of khaki uniform act as an effective disguise." The preponderance of Graves' syndrome in women is accepted by all.

Constitutional factor.—Neurocirculatory asthenia does not affect perfectly normal persons, nor does it arise de novo in such. Most observers[4, 6-10, 23] speak of a constitutional factor. This is evident in the extraordinary frequency of familial incidence. Oppenheimer and Rothschild[10] found "nervousness, insanity, or epilepsy in the family in 45 per cent." Wood found a high incidence of psychoneurosis or cardiac neurosis as compared to controls. Parkinson[8] found a family history of symptoms similar to those of neurocirculatory asthenia in 60 per cent of his cases. This does not necessarily imply that there is a genetic factor; far more likely, the transmission to the son is the result of environmental background and sensitizing factors. Thus, Jones and Lewis[9] found that a large majority of the victims were "spoiled" children, and that the horror of war was often inculcated by the parents. Wood found that, in childhood, most of the patients were delicate, and clung too long to their mothers' skirts. They were filled with apprehension about going to school, and, altogether, the case histories suggested that parental influence induced timidity.

The previous history offers further evidence of the constitutional factor in neurocirculatory asthenia. Most observers agree that the majority present a history of either neurocirculatory asthenia or psychoneurosis before enlisting, often dating back to adolescence. Thus, Oppenheimer and Rothschild found, in 75 per cent of their cases, a history of either stigmata, previous nervousness, fear, moodiness, a previous breakdown, enuresis, frights in childhood, or any of a number of other factors. Boas[23] found that the vast majority gave a history of nervousness and excitability dating back to childhood, and that they could not stand the strain of excitement. They bore a strong resemblance to the cases described by Bass and Wessler[24] in children, many of whom had orthostatic albuminuria. Wood[7] expresses himself similarly, and find that tics, bed-wetting, nightmares, and stammering are common traits, and that a psychiatric diagnosis, such as a depression, an anxiety state, hypochondriasis, hysteria, etc., could always be made. Jones and Lewis[9] obtained a history of stammering, bed-wetting, and sleepwalking in about 50 per cent, and nearly two-thirds were shy, tense, hypochondriacal, or delinquent. Parkinson[8] found that 50 per cent gave a history of symptoms similar to neurocirculatory asthenia before the war, but not sufficient to prevent them from pursuing their sedentary occupations. Observers are unanimous in their opinion that these patients are exceedingly sensitive to both physical and psychic influences, and are introvert and fearful. There are no anthropologic characters that are peculiar to patients with neurocirculatory asthenia, but most observers agree that they are not athletic in build, action, or spirit.

Taken by and large, there is sufficient evidence of a constitutional factor, and the probability is strong that it is phenotypic rather than genotypic.

These constitutional factors of neurocirculatory asthenia parallel those of Graves' syndrome closely. In a previous communication,[20] one of us pointed out the illuminating significance of a family history in Graves' syndrome. The same malady affects two or more members of the family, which is more than the law of averages allows.[26-28] What is especially striking is that few of the siblings are phlegmatic or adjusted folk; psychoneuroses of all sorts, cardiac neuroses, and even psychoses[29] are frequent, and the symptoms and signs are identical with those of neurocirculatory asthenia.

One of us also called attention to the fact that Graves' syndrome almost always affects persons of a characteristic psychic make-up. They are unusually sensitive and emotional. They respond to their environment, whether physical or psychic, like an aeolian harp, and, in consequence, feel that their lives have been unusually hard. Their emotional range is wide, varying from ecstasy to depression, and, indeed, psychoses of this nature are by no means uncommon.[30-32] Occasionally, one sees what appears to be a phlegmatic person with Graves' syndrome,[33] but, when one digs deeper, one finds that it is only a mask. This personality long antedates the onset of the disease, even back to childhood, and, moreover, persists after the grosser manifestations of Graves' syndrome have subsided.

These two factors, the familial and the personality, comprise the constitution of Graves' syndrome, and from the study of numerous patients from a psychoanalytic viewpoint,[34] we came to the conclusion that the influences that engender this constitution are environmental or the result of parental overprotection, rather than genotypic. That a genetic factor plays a role in the development of Graves' syndrome is indicated by the frequency with which the thymicolymphatic constitution is present. In the Mt. Sinai Hospital, it was found in over 90 per cent of our cases in which there was a fatal outcome. Warthin,[35] in particular, emphasized this factor. Whether this lymphatic constitution exists in neurocirculatory asthenia, we have no means of telling. The relation of this constitution to Graves' syndrome is not clear. Inasmuch as it is well known that persons with the lymphatic constitution are unusually sensitive to both psychic and physical stimuli, this may act as a sensitizing agent.

Exciting cause.—Most observers of neurocirculatory asthenia in the army, especially in the present war, emphasize fear as the dominating factor in producing the disease.[6-11, 36] The fear is of two kinds: (1) sudden, from some harrowing war experience such as gassing, shell explosion, etc., or (2) anticipated: Wood and Parkinson found that the fear of killing or of being killed was present in the majority of

their cases. Highly significant in this connection is the statement of Cohn,[36] who, in his inspection of the base hospitals in the week after the armistice, found only rare instances of neurocirculatory asthenia, whereas previously they had been common. Parkinson[8] found that neurocirculatory asthenia was rare in the Navy and Air Forces, for the reason that there is a greater proportion of volunteers in these services. In neurocirculatory asthenia of civil life, Craig and White,[22] in a study of 100 cases, found that psychogenic factors such as anxiety, sexual irregularities, an unhappy marriage, pregnancy, menopause, infections, and operations were frequent precipitating causes. In the last World War, some observers believed that neurocirculatory asthenia occasionally followed an infection,[6,10] In the present war, comment is singularly wanting on this score. Thus, Wood,[7] with his large experience, feels that the factor of infection is highly unimpressive, and that, when such a history exists, it is the fear engendered by the infection rather than the infection itself that is responsible.

These observations on neurocirculatory asthenia again parallel those in Graves' syndrome. That emotional crises may precipitate an attack of Graves' syndrome is well known. Indeed, we have observed the malady attain its full fruition within a few days after such a crisis. Among the precipitating events, we recall a robbery, a fire, the death of a close relative (usually a mother), a difficult confinement, a frightful sexual experience, a sudden economic loss, and an unwanted pregnancy. There was a sudden crop of Graves' syndrome in Vienna after the theater horror in the eighties, and after the San Francisco earthquake. We at the Mt. Sinai Hospital have been particularly struck with the frequency of Graves' syndrome among German refugees, so that the expression "Hitler Graves' " has come into vogue. The essential ingredients in these emotional crises are surprise and fear.

Frequently, one does not obtain any history of a surprise shock in Graves' syndrome. In these cases one usually finds reiteration of smaller and petty insults, or a new situation to which the patient cannot adjust himself, such as an unhappy marriage, a sexual abnormality, unrequited love, economic strain, etc. In these instances, it is often difficult to decide when the transition from the constitutional to the florid phase of the disease occurred. In Graves' syndrome, as well, infection has often been accused of precipitating an attack, but, in our experience,[20] as in Wood's in neurocirculatory asthenia, it is not the infection, but the fear induced (even when the infection is trivial) that is the significant factor.

Basal Metabolism.—Thus far, we have paralleled neurocirculatory asthenia to Graves' syndrome. It is now necessary to reverse the process because Graves' syndrome contains certain clinical elements which are usually absent in neurocirculatory asthenia, namely, an elevated basal metabolic rate, thyroid enlargement, exophthalmos, and

response to iodine. Inasmuch as the development of these features bears a relation to the evolution of Graves' syndrome, a discussion of the biology of this disease is in order. In a previous paper,[20] one of us tried to show that Graves' syndrome does not represent a nosological entity in the sense that it has a well-defined group of signs and symptoms and a consistent background in morbid anatomy, but rather a series of diseases arranged in biologic sequence that have previously received different names. The larval phase is the constitutional stage, which has been called Basedowoid, autonomic imbalance, pre-Basedow or pre-Graves', cardiac neurosis, neurasthenia, etc. The signs and symptoms resemble those of neurocirculatory asthenia so closely that they have often been confused. In the middle phase of the disease, at which time thyroid enlargement and perhaps lid-lag have been added to the other signs, the malady has been called a forme fruste. The final or florid phase consists of the classical quadrad of signs, plus an elevated basal metabolic rate, and is conventionally termed Graves' "disease." Between the initial and final phases one finds various groupings of signs and symptoms; one or more of the quadrad of signs, such as thyroid enlargement and exophthalmos, may even be missing. Graves' syndrome may be described as a hyperkinetic disease in which many of the physiologic functions are exaggerated. Because of this evolution and the inconsistency of the signs and symptoms, the term syndrome seems preferable. The common denominator in all these groups is the type personality described above, and the proof of this natural history, or life cycle, is not only the fact that, when the opportunity arises (and only the general practitioner has it), one can observe such transitions, but also, and more frequently, regressions to the larval phase under the influence of either spontaneous remission or treatment. The difference between the initial and florid phases of Graves' syndrome is like that between the tadpole and the frog. It is still the same animal, but of different shape and habits.

In most quarters, elevation of the basal metabolic rate is regarded as the vital diagnostic difference between Graves' syndrome and all other conditions that simulate it, and for this reason the terms Graves' syndrome and hyperthyroidism have been used interchangeably. We believe this is entirely arbitrary, and has perpetuated a fallacy that has contributed much to the existing confusion concerning the nature of Graves' syndrome. Because the basal metabolic rate is *usually* elevated in Graves' syndrome, one is not warranted in concluding that the patient does not have Graves' syndrome because the basal metabolic rate is *not* elevated. This error in reasoning is regrettably common in clinical medicine. The basal metabolic rate in thyroid disease measures only the degree of the hyperthyroidism, but Graves' syndrome comprises elements that are not entirely explained by the elevation of the basal metabolic rate alone, and for the following reasons: (1) Patients with "spent" or "burnt-out" Graves' syndrome, who reveal the classical

quadrad of signs, may possess a basal metabolic rate within the normal range. This does not imply that at some previous date the basal metabolic rate was not high; it probably was, but, clinically, such patients cannot correctly be said to have hyperthyroidism. Kessel and Hyman[12] classify such patients as cases of "autonomic imbalance," but we believe it would be more logical to call the condition "Graves' syndrome without hyperthyroidism." (2) After subtotal thyroidectomy, when the basal metabolic rate becomes normal, many of the clinical manifestations may persist for years, even though the patient is economically and socially restored. (3) During the larval or middle phases of Graves' syndrome, the basal metabolic rate is usually normal, but when, under an emotional strain, the disease assumes a florid form, with a rise in basal metabolic rate, are we justified in assuming that a different disease has been born? All we may say is that the patient has acquired hyperthyroidism. (4) The administration of toxic doses of thyroid extract to human beings mimics, but by no means completes, the clinical picture of Graves' syndrome. One obtains tachycardia and tremor and even weight loss, but no exophthalmos or swelling of the thyroid gland. In animals, Carlson[27] found that excessive doses of thyroid caused only loss of weight, gastroenteritis, and diarrhea. (5) Cases in which there are clinical evidences of Graves' syndrome associated with myxedema occur, even if but rarely. They usually represent exhaustion phenomena.[35-40] Sattler[27] cites a number of instances in which Graves' syndrome was engrafted on myxedema. Hyperthyroidism, as measured by the basal metabolic rate, may be regarded as the most important sign of Graves' syndrome, and it is to the reduction of this rate to normal levels that therapeutic efforts are largely devoted. It is a sign of activity comparable to fever in infections; when the temperature of a patient with typhoid fever returns to normal, he has not necessarily lost his disease. There is abundant evidence[5, 26, 35, 41, 42] that Graves' syndrome is by no means a disease exclusively of thyroid origin. The hyperactivity of the thyroid gland is only a link in the complicated mechanism whereby the disease arises, probably by way of the vegetative nervous system, with involvement of some of the other endocrine glands as complicating factors. The diagnosis of Graves' syndrome should not be dependent upon one or even a group of signs or symptoms, but upon a study of the total organ-personality. Evidence is accumulating rapidly that it is a psychosomatic disease[43-45] and a disease of the higher civilizations. Most observers agree that it is absent in primitive races.[41, 45] Particularly illustrative in this connection is the observation that, whereas formerly Graves' syndrome was extremely rare in Negroes, it is at present by no means uncommon, at least in our experience, among northern Negroes. We believe this increase is the result of industrialization and the production of increased conflict that they have acquired in their contact with whites.

If these points of view are accepted, it renders many of the curious, reported inconsistencies concerning the relation of neurocirculatory asthenia to Graves' syndrome understandable. For instance, numerous writers[50-53] report the association of neurocirculatory asthenia with Graves' syndrome because symptoms of neurocirculatory asthenia remain after thyroidectomy. In our experience, this is more common than is usually estimated. Our interpretation is that thyroidectomy does not cause a divorce between two separate diseases, but only between the hyperthyroidism and the neurocirculatory asthenia. In other words, thyroidectomy simply modifies the clinical picture by causing a regression to the larval stage. On the other hand, reports of an elevated basal metabolic rate in neurocirculatory asthenia are by no means infrequent. The incidence would probably be much more common were it not that most observers begin with a prejudice based on preconceived criteria of both diseases. As soon as the basal metabolic rate is found to be elevated the possibility of neurocirculatory asthenia is promptly excluded. Peabody, Wearn, and Tompkins[54] report the results of measuring the basal metabolic rates of 59 patients with ''irritable heart of soldiers.'' It was within 10 per cent of normal in 48 cases, and within 15 per cent in 53. In two cases, it was 60 and 61 per cent above normal. These were regarded as cases of Graves' syndrome. In three cases the basal metabolic rate was 16 to 22 per cent above normal. These latter cases were not regarded as Graves' syndrome.

A number of observers are puzzled by ''borderline'' cases between neurocirculatory asthenia and Graves' syndrome, i.e., patients who present most of the clinical evidences of Graves' syndrome, including tachycardia, tremor, exophthalmos, and goiter, but have a normal basal metabolic rate.[35, 50-52] We believe this quandary would vanish if the distinction between hyperthyroidism and Graves' syndrome were recognized.

Thyroid Enlargement.—That thyroid enlargement is not essential in the diagnosis of Graves' syndrome is attested by the frequency with which it is absent. It is difficult to estimate the exact incidence because this sign is subject to individual interpretation; according to different observers it varies between 25 and 50 per cent. Data in regard to thyroid enlargement in neurocirculatory asthenia vary widely. Thus, Sir Thomas Barr[2] found it in all cases of ''soldier's heart;'' Kessel and Hyman[12] found it in 72 of their 86 cases of ''autonomic imbalance;'' Brooks,[3] who leaned strongly toward the view that neurocirculatory asthenia and Graves' syndrome are identical, found a prominence of the thyroid gland in two-thirds of his cases. Boas[23] and Lewis[6] found that 4 per cent of the patients in their series had palpable thyroid glands. McCullagh[56] stated that thyroid enlargement occurs often; Crile[18] took a similar view. Kerr and Addis[57] found that the incidence of thyroid enlargement in recruits with neurocirculatory asthenia was

no higher than in a series of controls. Craig and White[22] found only 2 per cent with goiters. This wide variability among different observers affords opportunity for a number of reflections: (1) The confusion in the standards of diagnosis; (2) that the two maladies overlap; (3) that different phases of Graves' syndrome were being observed. Under any circumstance, the absence of thyroid enlargement in the early or neurocirculatory phase of Graves' syndrome does not exclude the diagnosis of Graves' syndrome, because one sees, all too often, the development of goiter in such patients. In other words, it is a later sign of Graves' syndrome. It would be equally valid to claim that, when albuminuria arises in the course of essential hypertension, a new disease has been engrafted. The probability is very strong, therefore, that Kerr and Addis[57] observed their cases in the larval phase (recruits), and that Kessel and Hyman[12] saw theirs in the later stages (hospital) of the malady.

Exophthalmos.—As with goiter, exophthalmos is also a symptom of the later, often the terminal, phase of Graves' syndrome. In genuinely florid cases, it is occasionally not present at all—according to Rienhoff,[29] in about 50 per cent. Nevertheless, it is interesting to note that what may be regarded as initial evidences of this sign are frequently seen in neurocirculatory asthenia. Thus, Sir Thomas Lewis[6] describes, as characteristic, the look of "frozen fear with wide eyes," and Barr,[2] the larger visible area of the sclera. Lewis also admits that "a few developed ocular signs." In the constitutional phase of Graves' syndrome, one of us has described widening of the palpebral fissure and lid-lag as common accompaniments, especially under excitement or even on moderate emotion. Kessel and Hyman,[12] in their series of eighty-six cases of "autonomic imbalance," found a von Graefe sign in nineteen and exophthalmos in twelve. Brooks[3] found that exophthalmos was common. Apparently, the status of exophthalmos as a differential criterion between neurocirculatory asthenia and Graves' syndrome depends, like the basal metabolic rate and thyroid enlargement, upon the phase of the disease in which the patient is observed.

Response to Iodine.—Most observers agree that iodine is of no avail in neurocirculatory asthenia, and, similarly, that it is useless in Graves' syndrome without hyperthyroidism. For this reason, the type of response to iodine in the two conditions, as some claim,[58, 59] cannot be deemed a diagnostic criterion.

Transition of Neurocirculatory Asthenia to Graves' Syndrome.—If, as we contend, these terms represent the initial and final phases of one and the same disease, why is it that most observers of the "irritable heart of soldiers" report such transitions but rarely? Rothschild[60] and Boas[61] did not see a single instance. There are a number of explanations for this discrepancy: (1) That the diagnosis was based upon the absence of clinical data rather than on their presence—data which became manifest

only in the later stages of the disease. Persons with frank cases of Graves' syndrome were usually not inducted into military service, and when, by chance, they were, they probably were excluded from study. Graves' syndrome was common enough in the past war, both in military and civilian circles,[28, 62-67] but, as far as we are aware, no study of this disease from the dynamic viewpoint was made. (2) There was insufficient follow-up. The only such study of neurocirculatory asthenia that is available is Grant's,[68] who reported the follow-up of 665 patients who had been observed in the Colchester Camp for the study of the effort syndrome. None developed Graves' syndrome. This is hardly surprising in view of the fact that they had been noncombatants and the war had ceased. This leads to the third explanation. (3) That the malady lost its momentum because the stimulus, fear, was eliminated by the cessation of the war, and protective mechanisms (institutionalization) were invoked. This factor is, by all odds, the most likely. As circumstantial evidence, we cite again the statement of Cohn,[36] who, in the week after the armistice, found neurocirculatory asthenia rare, whereas it had previously been common; in addition, we wish to call attention to the sudden diminution of articles on neurocirculatory asthenia in the *Index Medicus* after the cessation of hostilities, and the sudden rise with the onset of the present war. Curiously, nearly all of the reported cases in which such transitions were noted are in the literature concerning neurocirculatory asthenia in civil life,[18, 50, 53, 56] which can only mean that these observers were in a better position to recognize transitions.

The following eleven cases, observed in the Mt. Sinai Hospital during the past eight years, are reported. In our opinion, the number of cases is significantly large when we consider that they occurred in a hospital where transitions perforce cannot be observed as frequently as in private practice. The number is too large to be subject to the mere law of chance. We would undoubtedly have been able to report many more instances of transition had we been less rigid in our interpretation of the previous history, in which, although the clinical evidences of neurocirculatory asthenia were patent, basal metabolic readings were unavailable. The main reason transitions are not more frequently seen is the protection that envelops the patient as soon as the diagnosis of neurocirculatory asthenia is made. He is more or less shielded from, and rendered less amenable to, tribulation.

REPORT OF CASES

H. L. (Adm. No. 374074) was admitted to the hospital in December, 1934, with a well-defined Graves' syndrome. She had been under the observation of one of us since 1925 because of classical neurocirculatory asthenia. She had been very "nervous throughout her youth, and, with the advent of adolescence, was subject to frequent crying spells, baseless apprehension, and frequent attacks of palpitation. She married at 23 years but her husband's long absences and suspected in-

fidelities increased her instability. The birth of her only child, when she was 25 years old, brought complete absorption, with some recession of her symptoms. When, however, the child was old enough to go to school the enforced loneliness brought a marked exacerbation of the palpitation, sweats, and breathlessness. When first seen by us she presented a flushed facies, a very labile pulse rate and blood pressure, extreme hyperreflexia, and a marked anxiety state. Aside from its rapidity, the heart disclosed no abnormality; no murmurs were audible and the electrocardiogram was negative. There was slight, diffuse enlargement of the thyroid. The basal metabolic rate ranged from minus 10 per cent to plus 8 per cent. Sedatives and superficial psychotherapy, with some degree of cooperation on the part of the husband, brought temporary improvement. She was admitted to the Sydenham Hospital in June, 1931, where all investigations were negative and the basal metabolic rate was minus 6 per cent. With sedatives and rest in bed, the pulse rate became stabilized at 70. She was discharged with the diagnosis of neurocirculatory asthenia. In the latter part of 1933, she was deserted by her husband, and was forced to go on relief. Loss of weight, increasing nervousness, bulimia, increase in the size of the thyroid, and intense intolerance to heat appeared. She then presented the picture of Graves' syndrome, with exophthalmos, tremor of the fingers, a persistently rapid pulse, increased pulse pressure, and a markedly enlarged thyroid gland. The basal metabolic rate was plus 55 per cent. She was admitted to the Mt. Sinai Hospital in December, 1934, and had several brief attacks of paroxysmal auricular fibrillation during treatment with iodide. A two-stage subtotal thyroidectomy was performed, and the histologic appearance was that of a "follicular colloid adenoma with areas of hyperplasia." The symptoms and signs ascribable to the Graves' syndrome subsided rapidly. The emotional instability, pulse lability, and breathlessness are still present, with prompt accentuation under stress. The basal metabolic readings have remained normal until the present time (December, 1942).

W. McD. (Adm. No. 388170), a 30-year-old, married, billing clerk, was admitted to the Mt. Sinai Hospital Dec. 26, 1935, complaining of precordial oppression, nervousness, palpitation, and fatigability which, although present since early youth, had in the preceding eight months become considerably increased; additional recent symptoms were tremor, bulimia, and a loss of 20 pounds in weight.

He gave the following personal history when he first consulted the referring physician in 1928. He was the only child of apparently totally mismated parents, and his mother was twelve years his father's senior. His childhood was very unhappy; his mother was totally unsympathetic and manifested her resentment of him in a great many ways. The care of his father, who was rapidly becoming blind, fell entirely on the boy. At 13 years of age, after a rapid succession of conflicts at home, he first noted breathlessness, pounding of the heart, and nagging precordial sensations. He attended a commercial high school, but was compelled to leave six months before graduation and find a job, because his father was no longer employable. He became a bookkeeper in an uncle's business, but keenly felt his inability to complete school. He hated his work, and even minor responsibilities produced a sense of panic. Constantly criticized and frequently berated by his uncle, the attacks of breathlessness and palpitation became more frequent. A love affair, at 22 years of age, was finally terminated by

the girl's parents after several years because of religious differences; her marriage, shortly thereafter, to another induced a profound and prolonged depression; he became totally disinterested in his surroundings. The cardiac symptoms increased in severity, and for several months he did not venture from his home. A physician assured him that he had no evidence of heart disease, and suggested rest in the country, which brought temporary improvement. Repeated basal metabolism measurements ranged from minus 10 per cent to plus 6 per cent. He then secured a position as a billing clerk, which he still holds. He has since condemned himself bitterly for not having left his family sooner. At 28 years he married, after a brief courtship, but it brought him neither kindness nor understanding. Within the first year of marriage his mother died of gangrene of the extremities, his father committed suicide, and his wife bore a child which she did not want. The discord which marked his marriage abetted his sense of inadequacy. His sexual adjustment was poor.

About eight months before entering the hospital, his symptoms increased, palpitation became almost constant, intolerance to heat became pronounced, there was a marked tremor of the fingers, and he lost 20 pounds in weight despite the fact that he maintained his appetite. On examination he presented the classical picture of Graves' syndrome. He was hyperkinetic and asthenic. There were a distinct stare, moderate exophthalmos, and a fine tremor of the fingers. The pulse rate, although labile, rarely fell below 100 beats per minute. A distinct bruit and thrill were present over the diffusely enlarged thyroid. The heart sounds were dynamic; the systolic blood pressure was 146, and the sounds were audible down to 0. The skin was moist, the palms were warm, and there was a marked tache. Thrills were felt along the larger peripheral vessels. The basal metabolic rate was plus 59 per cent, but fell after treatment with iodide, to plus 22 per cent within ten days. Thyroidectomy was performed, with the removal of at least seven-eighths of each lateral lobe. The postoperative course was smooth, and, on discharge, the basal metabolic rate was plus 2 per cent and the blood pressure was 120/76. The pathologic specimens disclosed "(1) hyperplastic thyroid, as seen in Graves' disease, and (2) a small piece of parathyroid and thymic tissue."

He was observed at frequent intervals until the present time (November, 1942). Although the symptoms and signs of Graves' syndrome have completely disappeared, he reverted to the status preceding the onset of thyrotoxicosis. Emotional instability persists, as well as the cardiac sensations, tachycardia, flushing, apprehension, and hyperhidrosis; fatigability on even slight effort is pronounced. Repeated measurements of the basal metabolic rate have been normal.

D. F. (Adm. No. 406769), a 47-year-old housewife, was admitted to the hospital April 7, 1937, with a history of extreme nervousness since early youth. Vague precordial oppression, dyspnea, and palpitation would appear under any emotional stress. In the preceding ten years, her nervousness and excitability had increased considerably. About ten months earlier the patient had witnessed a robbery, which produced an hysterical state, with recurrent phobias and anxieties; she was compelled to remain in bed for several weeks. Crying spells were frequent. The events surrounding the robbery constantly reverted to her mind. She had been followed for several years in the surgical and medical clinics, and repeated examinations, including basal metabolic readings, were

negative. Because of trembling of the right arm of four months' duration, Parkinsonism was considered, and she was admitted to the Neurological Service.

On examination, she was short and squat. The neurologic status proved to be entirely normal, and the trembling of the right arm, which soon disappeared, was interpreted as a manifestation of conversion hysteria. There was a firm, grape-sized nodule in the right lobe of the thyroid. The pulse rate was 68; the blood pressure was 130/80. The heart disclosed no abnormality. She presented a flushed facies, mottling of the neck and chest, and marked sweating of the hands and feet.

After her discharge from the hospital, she was carefully followed, and the anxiety state persisted; any emotional crisis would precipitate breathlessness, precordial oppression, sweating, and palpitation.

In November, 1938, she began to lose weight, her appetite increased, and her previous symptoms were accentuated. The death of her mother, after thyroidectomy, shortly before her readmission to the hospital, on May 8, 1939, added to her apprehension. On examination she presented a well-defined Graves' syndrome, with exophthalmos, marked bilateral tremor of the fingers, persistent tachycardia, bulimia, and a weight loss of 22 pounds. Urinary frequency and diarrhea were pronounced. The basal metabolic rate was plus 46 per cent. With iodide treatment, the pulse rate fell from 120 to 70 and the basal metabolic rate to plus 14 per cent. Subtotal thyroidectomy was performed seventeen days after admission, and histologic study revealed a "hyperplastic thyroid with areas of colloid, as seen in Graves' disease." The thyrotoxic symptoms rapidly subsided after operation. She was not followed thereafter.

L. H. (Adm. No. 441026), a 40-year-old German refugee physician, was admitted to the hospital May 6, 1939, with Graves' syndrome. During the preceding five months there had been increasing enlargement of the neck, a loss of 30 pounds in weight, extreme nervousness, tremor, palpitation, and bulimia.

Since early youth, he had been very introspective, easily frightened, and apprehensive. In high school he would experience violent palpitation and dyspnea when called upon to recite or during examinations. He was told that, when frightened, his skin would assume a subicteric hue. With the advent of the Hitler regime his symptoms became more pronounced, with almost constant palpitation, precordial oppression, fatigability, and irritability. Holidays and sedatives would bring transient relief. The basal metabolic rate was normal on several occasions.

On examination he was hypermotile, and there were a distinct stare and lid-lag. The left lobe of the thyroid was enlarged to the size of a lemon. The heart rate varied from 96 to 110 beats per minute. The blood pressure was 146/68. The spleen was enlarged 2 fingerbreadths below the free border of the ribs. A chest roentgenogram disclosed moderate extension of the thyroid into the left upper part of the mediastinum. The basal metabolic reading on admission was plus 40 per cent, and fell to plus 12 per cent after nine days of treatment with iodide. Subtotal thyroidectomy was performed, and histologic examination disclosed a hyperplastic thyroid, as seen in Graves' disease. The postoperative course was uneventful.

The picture of neurocirculatory asthenia has not, however, been significantly altered, and he still responds to difficult situations with palpitation, precordial oppression, fatigability, and, at times, dyspnea.

Mrs. B. B. (Adm. No. 414655), a 59-year-old mother of two children, came under our observation in 1924, at the age of 41. She complained of a peculiar aching sensation in the precordium, palpitation, hyperhidrosis, and apparently baseless crying spells. Similar symptoms had been present since early childhood. She recalled that, when her father died suddenly when she was 6 years old, her mother made a constant companion of her, and she was subsequently entrusted with most of the household duties and care of the other children. These responsibilities often engendered a sense of inadequacy and panic, accompanied by trembling, sweats, and pounding of the heart. She would weep because of fancied slights, a tendency which persisted even after what was apparently a very happy marriage. Frequent examinations never disclosed any evidence of disease. The hands were constantly moist, cool, and bluish; the resting pulse rate was 72, and the basal metabolic rate varied from minus 10 per cent to plus 5 per cent. Her blood pressure fluctuated widely; it would reach 160/100, but promptly fall to normal on recumbency. When any member of her family fell ill her symptoms would multiply, with almost constant palpitation, precordial oppression, and dyspnea. A small thyroid adenoma appeared after the birth of her second child, when she was 24 years old, but never seemed to increase in size. Repeated cardiovascular studies failed to disclose any evidence of disease. The advent of the menopause at 49 years somewhat accentuated her vasomotor instability.

In October, 1926, she began to lose weight in spite of a tendency to bulimia. The heart rate rarely fell below 110, even during sleep, and the pulse pressure rose. A slight stare and lid-lag appeared. The basal metabolic rate was plus 48 per cent. In deference to her dread of operation, palliative measures were instituted, with temporary remission of symptoms, and the basal metabolic rate fell to plus 24 per cent. This was only transient, however, and, with the return of a severe Graves' syndrome, subtotal thyroidectomy was performed Oct. 6, 1937. The postoperative course was uneventful, with rapid diminution of the nervousness, hyperactivity, tremor, tachycardia, and bulimia. She promptly regained her lost weight.

During the last five years she has been under careful supervision, and there has been no return of the Graves' syndrome. The emotional instability and other symptoms identified with the neurocirculatory asthenia that she manifested prior to the appearance of the hyperthyroidism persist unchanged.

T. L. (Adm. No. 430214), a 35-year-old housewife, was admitted to the hospital (Dr. Baehr's service) Sept. 29 1938, at which time a diagnosis of neurocirculatory asthenia and anxiety neurosis was made. She had always been intensely sensitive, and had been subject to attacks of weakness, breathlessness, and palpitation since adolescence. At the age of 24 years, shortly after the birth of her second child, she had a severe "nervous breakdown," and was in bed for a month. Profound weakness, persistent palpitation, and hyperhidrosis persisted until she secured relief after a sojourn in the country. During the preceding four years, palpitation became more frequent, and appeared after but slight strain and lasted as long as three hours. The attacks began suddenly, with irregular pounding of the heart and frequent sharp precordial pain radiating to the interscapular region. In the intervals between attacks, she was unable to concentrate. She experienced generalized body tremors and was asthenic. There were also recurrent

attacks of dyspnea, suggesting "sighing respiration," which were un-related to the palpitation, and appeared chiefly when she was at rest. Diffuse sensations of warmth, followed by profuse sweating and chills, occurred several times daily. Excitement or fear, induced by trifling incidents, would precipitate severe diarrhea. Repeated measurements of her basal metabolic rate, made largely at the insistence of the pa-tient because her mother had had Graves' syndrome, ranged from minus 10 per cent to plus 12 per cent. On examination she was some-what apathetic. There was no exophthalmos or lid-lag. There was no tremor of the fingers. There was slight, diffuse enlargement of the thyroid. The pulse rate was labile, varying from 110 to 68. The heart sounds were loud and booming. The basal metabolic rate was plus 5 per cent. Psychiatric consultation disclosed the fact that she was an emotionally immature person who was almost completely dependent on her mother in spite of her marriage of eighteen years. She had never quite recovered from the trauma of her mother's death four years before. It was felt that there was a distinct psychogenic coloration to the attacks of dyspnea and palpitation, for they subsided promptly when she was relieved of her household responsibilities. Further ob-servation in the hospital failed to disclose any evidence of organic disease. The pulse rate became slow, the tremor disappeared, and there was no heat intolerance. Subsequent basal metabolic readings varied from plus 12 per cent to minus 10 per cent.

After her discharge from the hospital there was some amelioration of her symptoms; she gained weight and the attacks of tachycardia and breathlessness diminished both in frequency and intensity. She was carefully observed in the Out-Patient Department, and appeared to respond well to superficial psychotherapy. In the light of her patently improved status, the case was finally closed in January, 1940.

In June, 1940, almost immediately after a severe nervous shock, the nature of which she refused to disclose, her diarrhea returned and she had as many as eight movements a day; palpitation, precordial pain, intense nervousness, and an inordinate increase in appetite and ex-treme weakness appeared. The basal metabolic rate was plus 36 per cent. On readmission to the hospital on Aug. 16, 1940, she presented marked exophthalmos, tachycardia, with a constant rate of 110, ex-treme nervousness, and a blood pressure of 160/90. It was felt by the staff that she had Graves' syndrome, and, after preliminary iodide treatment, with a fall in the basal metabolic rate to plus 3 per cent, a subtotal thyroidectomy was performed. The resected gland was re-ported as "hyperplastic thyroid, as seen in Graves' disease in a colloid phase." The thyrotoxic symptoms diminished rapidly after operation.

She has been followed at intervals of a few months until the present time. Although she has gained twelve pounds in weight and the tremor, bulimia, and pulse rate lability have disappeared, the heart consciousness, sighing respiration, and precordial awareness persist.

R. S. (Adm. No. 434778), a 36-year-old housewife, came under the ob-servation of one of us in 1934, complaining of nervousness, palpitation, fatigability, and sweating, particularly under emotional stress. Al-though these symptoms had been present to a variable degree since adolescence, economic reversals after marriage and the care of two children with behavior problems accentuated her instability. In early youth she had several attacks of syncope, induced by either pain or fright. Two attacks of rheumatic fever, the first at 15 years and the

second at 26 years, necessitated many months in bed, but there was no complicating valvular disease. Repeated assurance that her heart was not affected scarcely diminished her apprehension and introspection. On examination, she presented a flushed facies and mottling of the neck and chest. The heart rate was labile and the sounds dynamic. The blood pressure was 118/84. The palms were cool and moist. Fluoroscopically, the cardiac configuration was normal, and the electrocardiogram was negative. The basal metabolic rate was minus 8 per cent. She was seen on several occasions in the next three years without any change in the clinical picture except for rapid improvement during vacations; the basal metabolic rate remained below normal. Therapy was limited to suggestion, reassurance, and sedatives.

About six months preceding admission, her husband's refusal to consider having another child led to an estrangement. Her symptoms rapidly increased, palpitation became almost constant, enlargement of the neck appeared, and, despite increased appetite, she lost 10 pounds in four months.

She was admitted to the hospital Jan. 11, 1938, with a classical Graves' syndrome. There were distinct exophthalmos, tremor of the fingers, hypermotility, a diffusely enlarged thyroid, and a basal metabolic rate of plus 44 per cent. The heart rate rarely fell below 110 beats per minute. The blood pressure was 156/84. The electrocardiogram disclosed the prominent P and T waves of Graves' syndrome. The palms were warm and moist. With iodide treatment the basal metabolic rate fell to plus 12 per cent, and a subtotal thyroidectomy was performed. Histologic examination disclosed a "hyperplastic thyroid, as seen in Graves' disease." The postoperative course was smooth, and the symptoms of hyperthyroidism subsided rapidly.

She has been seen at four-month intervals. The basal metabolic rate has varied from minus 12 per cent to plus 4 per cent. Although she has had a complete reconciliation with her husband, the nervous instability, intermittent palpitation, fatigability, and heart consciousness that she manifested before the onset of the Graves' syndrome persist without significant change.

R. A. (Adm. No. 453642), a 25-year-old, married schoolteacher, consulted one of us in January, 1937, because of recurrent attacks of breathlessness, precordial oppression, palpitation, nervousness, and sweating. Nervous instability and intermittent anxieties had been pronounced since early childhood; she had been taken to numerous physicians who succeeded only partly in assuaging her fears that her heart was diseased and that death was imminent. Sighing respiration persisted through adolescence, but diminished when she was married at the age of 19 years. With the advent of pregnancy, 3 years before, all of her earlier symptoms returned with great intensity, but were abruptly terminated by the birth of a normal child. In the next two years, however, her child's many illnesses, a very difficult school class, and her husband's loss of his position induced a severe exacerbation of her instability. In spite of a diminished appetite, her weight remained stationary. On examination, she appeared well nourished but extremely apprehensive, and showed a well-defined autonomic imbalance. The pulse rate varied from 150 to 90; the palms were cool and moist; there was moderate, diffuse fullness of the thyroid; the heart sounds were dynamic, and the deep tendon reflexes hyperactive; the basal metabolic rate was minus 6 per cent. In spite of reassurance,

persuasion, and sedatives, her symptoms persisted, presumably because of increasing economic burdens and the severe illness of both her parents. Paroxysms of tachycardia, with the heart rate reaching 160 per minute, were precipitated by even mild irritation. These attacks were often promptly terminated by her physician's reassurance. Measurements of the basal metabolic rate, which were made frequently, largely because of the patient's insistence, varied from minus 10 per cent to plus 4 per cent.

In January, 1940, weight loss became evident, her appetite suddenly increased, and the resting pulse rate, which was previously about 70, rarely fell below 100. A distinct stare and a fine tremor of the fingers appeared. In the space of six weeks she lost 12 pounds and noted extreme intolerance to heat. The basal metabolic rate was plus 32 per cent. There had been amenorrhea for two months. There was a marked skin tache, and the palms of the hands, previously cold and moist, became quite warm. The thyroid had enlarged considerably and was firm. She became pregnant in February, 1940, and was admitted to the Mt. Sinai Hospital March 12 for a therapeutic abortion because of active Graves' syndrome. A few hours after admission she aborted spontaneously. Iodide treatment was begun one week thereafter, and a subtotal thyroidectomy was performed April 6. Histologic study of the resected gland disclosed "hyperplastic thyroid, as seen in Graves' disease in the colloid phase." Convalescence was uneventful, and she was discharged to a rest home a week later.

She has been seen at frequent intervals since her discharge from the hospital. The basal metabolic rate is persistently normal. Although she presents none of the residua of the Graves' syndrome, the emotional lability, unstable pulse rate, heart consciousness, and hyperhidrosis persist.

S. S. (Adm. No. 456692), a 45-year-old German refugee housewife, was admitted to the hospital May 14, 1940, and, after a week's observation, diagnoses of neurocirculatory asthenia anxiety neurosis, psoriasis, and a possible anginal syndrome were made. She had been nervous since childhood, and had responded to difficult situations with palpitation and sweating. Dyspnea on exertion was first noted five months before admission, and was accompanied by mild precordial pain. Since coming to this country she had been compelled to do domestic work in addition to taking care of her own household. She was greatly concerned over a brother who was stranded in Europe. On examination she presented a moderately labile, variable pulse rate. A soft systolic murmur was audible over the pulmonic area. The edge of the liver was felt one fingerbreadth below the costal margin. There were many scattered psoriatic lesions on the skin. Several basal metabolic readings varied from plus 4 per cent to minus 10 per cent. Psychiatric consultation indicated that anxiety played the dominant role in her illness. She was approaching the menopause, was burdened with the usual problems besetting refugees, and she worried lest she develop Graves' disease, as her mother had done. The heart did not show any evidence of disease.

After her discharge from the hospital she showed moderate improvement for several weeks. Further psychic trauma, however, soon induced a return of all her former symptoms, with such additional complaints as an increased desire for food, persistent palpitation, constant nervousness, prominence of the eyes, and enlargement of the neck. She

was readmitted to the hospital Aug. 20, 1940, with the unmistakable picture of Graves' syndrome. The basal metabolic rate was plus 54 per cent. The thyroid was diffusely enlarged. A loud systolic murmur was audible over the entire precordium. The blood pressure was 154/70. After fourteen days of iodide treatment, the basal metabolic rate fell to plus 9 per cent, and a subtotal thyroidectomy was performed. The pathologic report was "hyperplastic thyroid, as seen in Graves' disease in the colloid phase."

Although disappearance of the thyrotoxic symptoms was rapid, the emotional instability was not significantly affected. Intermittent palpitation, flushing, and fatigability varied with the degree of her economic and social stability. She was readmitted to the hospital Jan. 6, 1941, for the removal of a lipoma of the breast. She presented a well-defined picture of neurocirculatory asthenia. The basal metabolic rate was minus 6 per cent.

H. F. (Adm. No. 458510), a 48-year-old married tailor, was admitted to the hospital Aug. 18, 1940, with the classical picture of Graves' syndrome. He first consulted one of us in March, 1934, at which time he complained of extreme nervousness, palpitation, sweating, fatigability, and aching precordial sensations, chiefly when under emotional stress. Two nervous breakdowns within the preceding five years induced prolonged incapacity. Marked nervous instability had been present since early youth. His environmental adjustments had been uniformly poor. His mother died in an institution for the insane, and he constantly dreaded a similar fate. He had never been able to earn a satisfactory livelihood. For more than eight years, he and his wife lived in furnished rooms and ate in cheap restaurants. During his "slow" seasons his symptoms diminished, only to be aggravated when he was compelled to work hard.

When first seen he presented a flushed facies, labile pulse rate, and hyperhidrosis; the examination was otherwise negative. The basal metabolic rate was minus 4 per cent. He was considered to be suffering from neurocirculatory asthenia, and was treated with reassurance, encouragement, and sedatives, occasionally. Improvement was variable, but he responded, as a rule, to superficial psychotherapy. He was seen at frequent intervals in the following six years, during which there was but little change in the clinical picture. Several basal metabolic readings were normal.

About eight months preceding admission he sustained a severe nervous shock, which was soon followed by a distinct change in his symptoms. Nervousness and palpitation became constant, a poor appetite was replaced by actual bulimia, he lost 15 pounds in weight, and intolerance to heat became pronounced. Substernal pain was induced by even mild exertion. On admission, he presented a distinct stare and lid-lag. The heart rate was 124 beats a minute. A plum-sized adenoma of the left lobe of the thyroid was continuous with a substernal extension, as revealed by roentgenogram. A harsh systolic murmur was audible at the apex. The basal metabolic rate was plus 32 per cent. With iodide therapy the rate fell to plus 10 per cent, and a subtotal thyroidectomy was performed. Histologic study of the resected gland disclosed a "hyperplastic thyroid, as seen in Graves' disease." Improvement after operation was very rapid, with prompt disappearance of the hyperthyroid symptoms. There has been no change, however, in the underlying neurocirculatory asthenia.

H. B. (Adm. No. 459771), a 40-year-old retail shoe dealer, entered the hospital July 13, 1940, with the classical picture of Graves' syndrome. He stated that he had been highly impressionable and sensitive since early childhood, rarely entered into the activities of his schoolmates, and was largely asocial. Shortly after his marriage, eight years before, nervousness and irritability became more pronounced. Attacks of emotional instability, accompanied by pounding of the heart, precordial oppression, and moderate dyspnea were precipitated by even minor conflicts or irritations; constipation was pronounced. He was studied by several physicians, but failed to find comfort in their negative examinations. Repeated basal metabolic readings were normal. In the preceding four years his complaints were persistent. In the last year, however, longstanding, stubborn constipation was replaced by a tendency to frequent and loose evacuations. Three months prior to admission to the hospital, he took over the added responsibilities of a larger business which necessitated gruelling work and long hours. He then noted rapid weight loss, persistent palpitation and dyspnea on but slight exertion, increasing nervousness, and enlargement of the neck. Prominence of the eyes had been but recently noted. The basal metabolic rate was plus 54 per cent.

On examination, he was hyperactive, with a distinct tremor of the fingers, a resting pulse rate of 110, a marked stare, and enlargement of the left lobe and isthmus of the thyroid. Aside from the tachycardia, cardiovascular studies were negative. Psychiatric investigation disclosed a frustrated, unhappy man, profoundly depressed by his insecurity and illness. With iodide therapy and sedatives, the basal metabolic rate fell from plus 46 per cent to plus 18 per cent, and a subtotal thyroidectomy was performed. Histologic study of the resected gland revealed a "hyperplastic thyroid, as seen in Graves' disease in the colloid phase."

He has been seen subsequently at frequent intervals. Although the basal metabolic readings have been consistently below normal (minus 4 per cent to minus 10 per cent), and there are no residual signs of the Graves' syndrome, the nervousness, palpitation, and dyspnea that he had experienced for many years preceding the onset of the disease have persisted without interruption.

SUMMARY

All evidences point to the psychosomatic nature of neurocirculatory asthenia. Neurocirculatory asthenia is by no means a disease incidental to war, and it is more common in women than men. Viewed from the dynamic and biologic aspects of Graves' syndrome, the similarity between neurocirculatory asthenia and the initial or larval phase of Graves' syndrome is so close that we believe the two are identical. Transitions of neurocirculatory asthenia to Graves' syndrome and the reverse are by no means uncommon. Eleven such instances are reported.

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FURTHER OBSERVATIONS ON THE DEEP Q_3 OF THE ELECTROCARDIOGRAM

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NEWARK, N. J.

PARDEE, several years ago, made a distinct contribution to clinical electrocardiography by directing attention to the deep Q_3. The criteria set up by him were as follows:

1. Q_3 must be at least 25 per cent of the largest excursion of QRS in any lead.
2. The record must not show right axis deviation.
3. R_3 must be present and S_3 absent.
4. QRS_3 must not be M- or W-shaped.

The original observations were made on persons who had, or were suspected of having, organic heart disease, as were also the studies that shortly followed. Soon afterwards, however, clinicians everywhere began to find deep Q_3's in the electrocardiograms of many persons who had no other evidence of heart disease, and came gradually to the conclusions that a high position of the diaphragm is a more important factor than had at first been supposed, and that a deep Q_3 is found in many cases in which there is no heart disease. This led, naturally, to efforts to distinguish between pathologic and positional deep Q_3's, which continue to the present time.

Some clinicians consider a deep Q_3 unimportant if it diminishes or disappears on deep inspiration, on the theory that, if it is so changed by the descent of the diaphragm, it must be due to position. Others consider it pathologic despite this variation, believing that any deep Q_3 can be made to disappear if the heart, by a change in position, can be brought into the proper relation to the electrodes.

Some clinicians place the chief emphasis on Q_2. If Q_2 is small or absent, they feel that Q_3 is probably of no significance. If Q_2 is relatively large, they consider Q_3 pathologic.

Another sign that has been used as a means of distinction is the tiny upward deflection, measuring 1 mm. or less, that sometimes precedes the downward deflection in Lead III. In the beginning, the weight of opinion seems to have been that a downward deflection that is preceded by a minimal upward deflection, either constantly or intermittently

throughout the record, is not a Q wave. Then, more and more observers came to be of the opinion that an upward deflection in some complexes does not take the subsequent downward deflection out of the Q class, and they fixed upon the rule that, if more than half the complexes are without the initial upward deflection, the downward deflection is still to be considered as a Q wave. Now, if one can judge from the illustrations in their latest books, some authorities ignore the upward deflection entirely, even if it occurs in every complex, and call all of the subsequent deflections Q waves.

DIFFERENTIATION BY UNIPOLAR EXTREMITY LEADS

More recently, Wilson has given us a new approach to this problem by the work he has done on unipolar extremity leads.

These leads are made by using the central terminal developed by Wilson and his associates as the distant electrode, and placing the exploring electrode on each of the three standard lead points, in turn—the right arm, the left arm, and the left leg.

The advantage of unipolar leads is that the exploring electrode measures potentials from zero, the potential of the central terminal. Consequently, a downward deflection, a Q or an S wave, means absolute negativity of the exploring electrode, and an upward deflection, an R wave, means absolute positivity. In contrast, the standard leads are bipolar leads, made with two electrodes equally capable of receiving impulses, and measure the difference in potential between those electrodes, so that positivity and negativity are relative. In the standard leads, Q, R, and S are merely descriptive terms without reference to origins.

The unipolar extremity leads combine to make up the standard leads, as follows:

$$\text{Lead} \quad \text{I} = V_L - V_R$$
$$\text{Lead} \quad \text{II} = V_F - V_R$$
$$\text{Lead} \quad \text{III} = V_F - V_L$$

where *minus* means add the mirror image, that is, turn the curve, on the isoelectric line as an axis, through a $180°$ angle, and add.

Wilson's application of the unipolar extremity leads to the problem of the deep Q_3 rests upon the fact that the ventricular cavity is negative throughout systole. He has demonstrated this by experiments on dogs, in which he thrust a stab electrode, insulated except at its tip, through the ventricular wall and took leads from inside the cavity. The QRS complex obtained in this way is monophasic and negative.

The negativity of the cavity may be seen in the normal electrocardiogram in the QRS complex of V_R, because, as the heart lies in situ, the right arm is opposite the base and receives the cavity effects through the valvular orifices. The QRS complex consists of a large downward deflection with, perhaps, a tiny upward deflection at the beginning or end

or both, representing a small positive disturbance from the sides. An infarct that involves the entire thickness of the ventricular wall produces no electrical currents: it is equivalent to creating another orifice. The cavity effects come through this orifice to produce a downward deflection, a Q wave early in systole. A posterior infarct, since it is turned toward the foot, produces a Q wave in V_F. An anterior infarct produces a Q wave in V_L.

Reference to the equations mentioned previously makes it clear why the Q wave in a case of posterior infarction shows in Leads II and III, and in a case of anterior infarction in Lead I. V_F enters positively into the equations for Leads II and III, that is, without inversion, so that a Q wave in V_F remains a downward deflection, a Q wave, in Leads II and III. V_L enters positively into Lead I, and its Q wave shows as a Q wave in Lead I, but it does not show in Lead III because V_L enters negatively into Lead III, and its Q wave becomes an upward deflection, an R wave, according to the descriptive terminology.

By the same reasoning it is clear that an initial downward deflection in Lead III may result either from a downward deflection in V_F or from an upward deflection in V_L turned upside down. Herein lies the confusion between the coronary deep Q_3 and the deep Q_3 that is due to position. The difference is illustrated in Figs. 1 and 2.

In Fig. 1, the deep Q_3 comes from an inverted R wave in V_L, and there is no Q wave of any significant magnitude in V_F. The subject was a man, 37 years old, who was considerably overweight (5 feet 8 inches, 210 pounds). There was nothing in his history to suggest coronary occlusion.

In Fig. 2, the deep Q_3 comes from a Q wave in V_F, augmented slightly by an inverted R wave in V_L. The subject was a man, 46 years old, who was not overweight (5 feet 8 inches, 163 pounds). On April 24, 1942, he had acute coronary occlusion, with classical symptoms. His electrocardiograms have shown serial changes characteristic of posterior infarction, namely, marked elevation of the S-T segments in Leads II and III, with the development of large Q waves which were not present previously; return of the S-T segments to the isoelectric level, with sharp inversion of the T waves in Leads II and III; and gradual return of the T waves toward normal, with persistence of the Q waves. The record shown in Fig. 2 was made Nov. 25, 1942.

It is the purpose of this paper to re-examine the various criteria defining and distinguishing the deep Q_3 from the viewpoint that Wilson has given us. We have not been able to gather enough cases to prove anything statistically, but we believe that the cases* shown illustrate certain fundamental principles.

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*All of these subjects are employees of The Prudential Insurance Company of America.

THE EFFECT OF INSPIRATION

The deep Q_3 in Fig. 1 is, presumably, due to position, for there was nothing in the history to suggest coronary occlusion; there is no Q wave in V_F, and there was marked obesity to explain it. The mechanism of
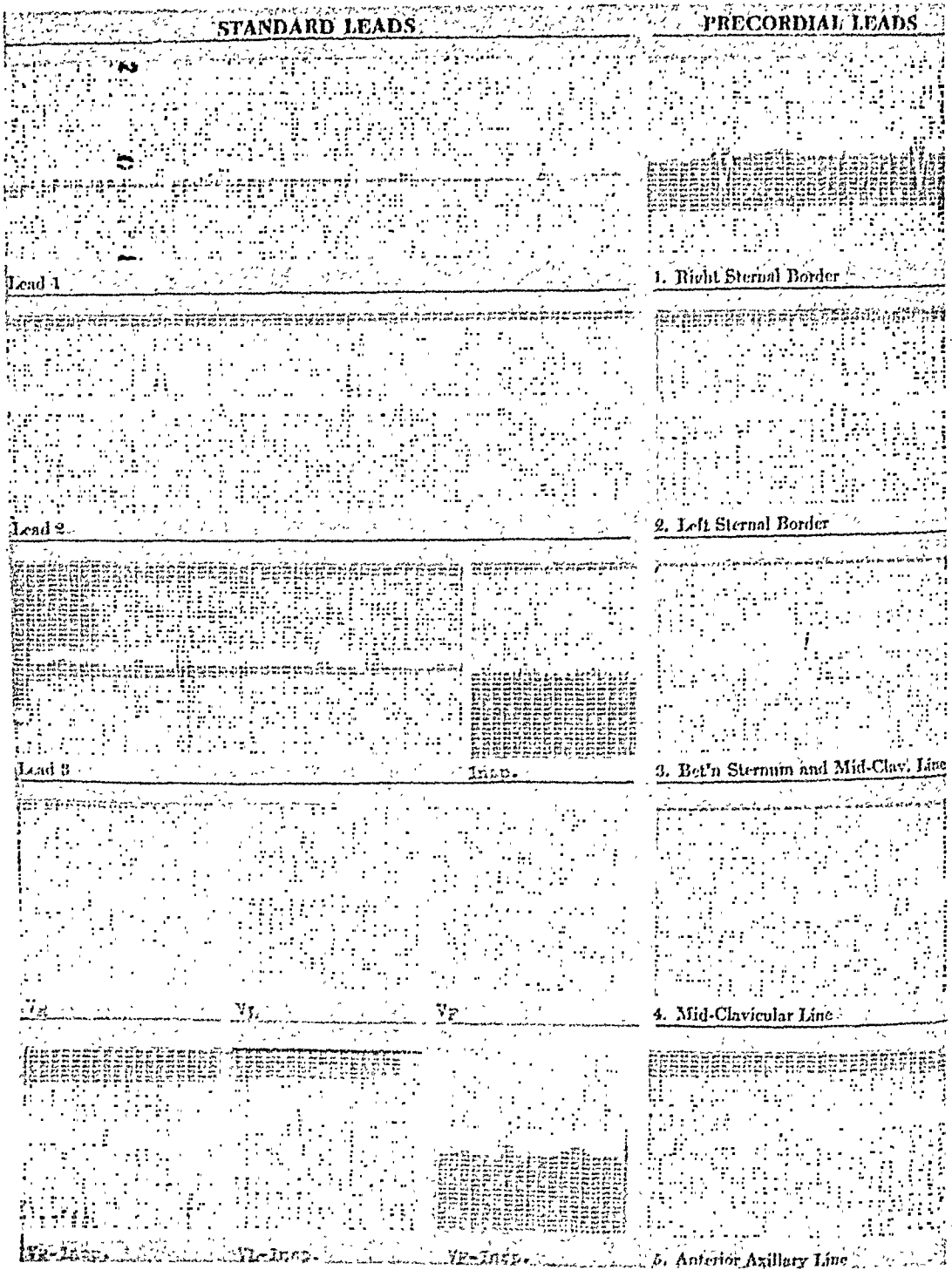
Fig. 1.

its disappearance can be seen to be the disappearance of the R wave in V_L on deep inspiration.

The deep Q_3 in Fig. 2 is, unquestionably, due to myocardial infarction. There was the typical history, supported by the serial changes in the
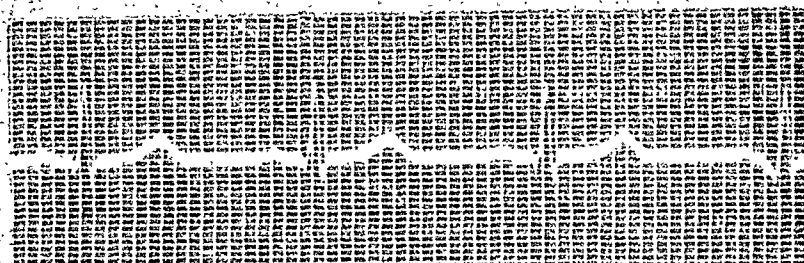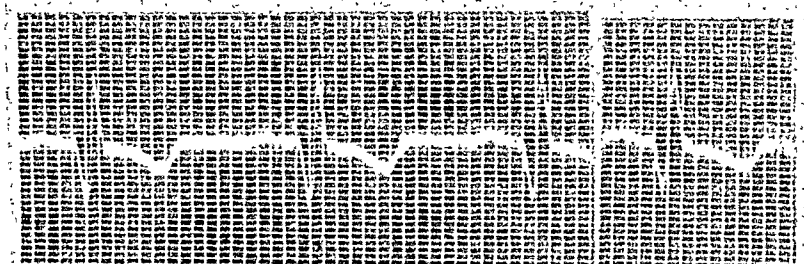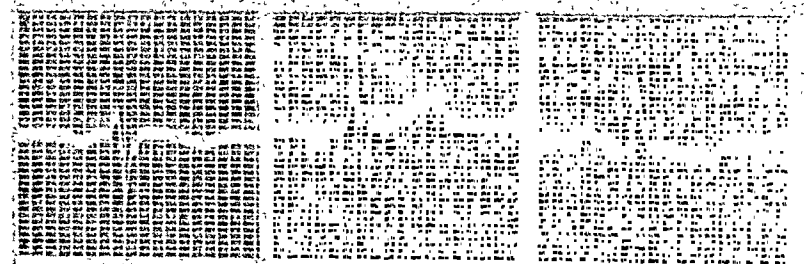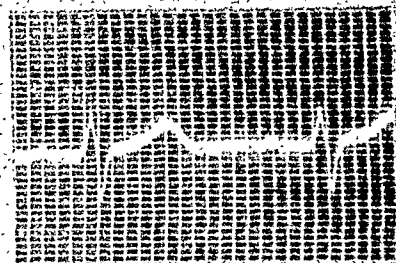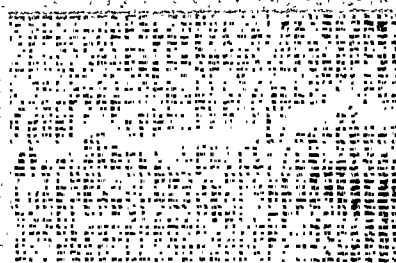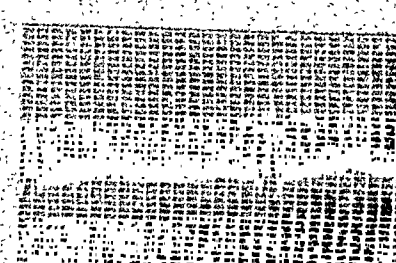
STANDARD LEADS		PRECORDIAL LEADS
Lead 1		1. Right Sternal Border
Lead 2		2. Left Sternal Border
Lead 3	Insp.	3. Bet'n Sternum and Mid-Clav. Line
VR VL VF		4. Mid-Clavicular Line
VR-Insp. VL-Insp. VF-Insp.		5. Anterior Axillary Line

Fig. 2.

electrocardiograms. There are absence of the deep Q_3 in previous electrocardiograms and its presence in the record made when the pain was at its height. There is persistence of Q_3 after other electrocardiographic signs have largely disappeared, and there is the abnormally large Q wave in V_F. Deep inspiration produces a slight diminution of Q_3, which has the same mechanism as in Fig. 1, namely, lowering of the R wave in V_L. It will be noted that the Q wave in V_F shortens little, if any, and that Q_3 does not become smaller than Q_F.

It would seem, therefore, that the disappearance of a deep Q_3 on inspiration does suggest a positional origin. It is difficult to see how sufficient rotation of the heart, in situ, could be produced by inspiration to turn the infarct away from the foot so that the Q wave would disappear in V_F.

In some cases in which there are no Q waves in V_F and no history suggestive of infarction (that is, cases in which the deep Q_3 is presumably due to position), we have been unable to make Q_3 disappear or to lower R_L by inspiration, so that its failure to disappear is still an equivocal observation.

THE 25 PER CENT RATIO

If the significant portion of Q_3 is that made by the Q wave in V_F, then it is evident that a coronary Q_3 may be less than 25 per cent of the maximum R wave, since Q_F is often augmented by R_L to give Q_3 its total depth. It is necessary to establish new criteria by studying V_F in a sufficiently large number of cases to ascertain the normal limits of its Q wave.

THE PRESENCE OF Q_2

Since V_F enters positively into the formation of both Lead II and Lead III, the presence in Lead II of a Q wave of sufficient magnitude is usually evidence enough that the Q_2 is due to a Q wave of significant proportions in V_F, although Q_2 may be somewhat increased by an initial upward deflection in QRS_R. A small Q wave in Lead II cannot, however, be taken as evidence that the Q wave is small in V_F, for V_R enters negatively into Lead II, and if the beginning of the downstroke in V_R is synchronous with Q_F it will cut down the Q wave in Lead II.

This is well shown in Fig. 3, in which Q_F is diminished in Lead II by an early downstroke in V_R and is augmented in Lead III by R_L. The subject was a man, 49 years old, who has complained of angina of effort since 1932. From the beginning, his electrocardiogram showed diphasic to inverted T waves, with slight depression of the S-T segment, in Lead I. On Sept. 26, 1941, he suffered an unusually severe attack of pain, lasting one hour, and, on Oct. 21, 1941, another, lasting two and one-half hours. After the second attack, his angina of effort was more pronounced and his electrocardiogram showed marked changes as compared with previous records. The T waves in Leads II and III and in all the precordial leads, which were formerly upright and of good voltage, were
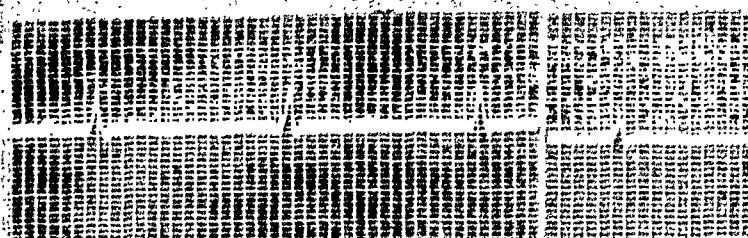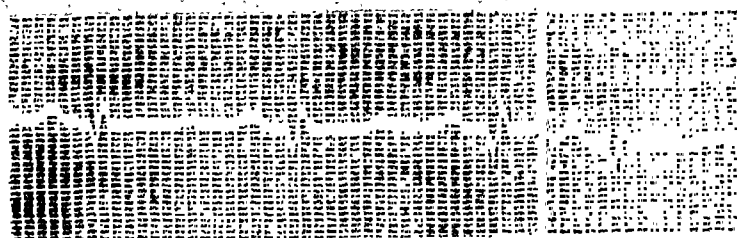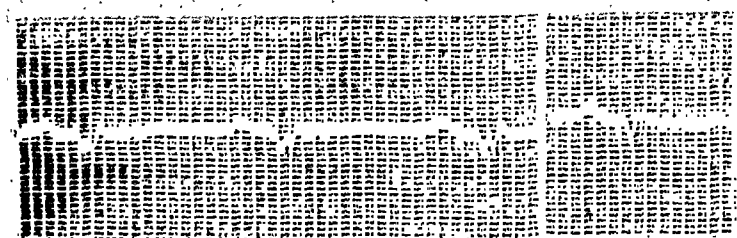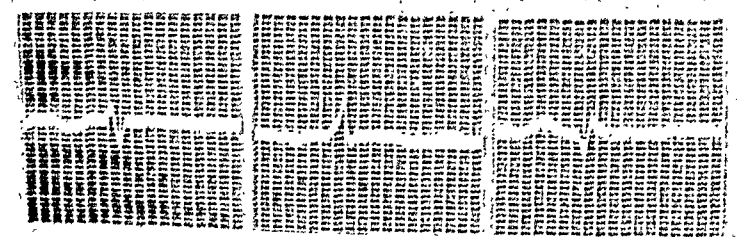
STANDARD LEADS | PRECORDIAL LEADS

Lead 1. / 1. Right Sternal Border

Lead 2 / 2. Left Sternal Border

Lead 3 / Insp. / 3. Bet'n Sternum and Mid-Clav. Line

VR / VL / VF / 4. Mid-Clavicular Line

VR-Insp. / VL-Insp. / VF-Insp. / 5. Anterior Axillary Line

Fig. 3.

STANDARD LEADS	PRECORDIAL LEADS

Lead 1   Insp.   1. Right Sternal Border
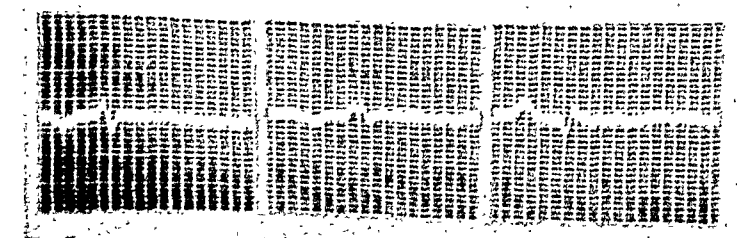
Lead 2   Insp.   2. Left Sternal Border

Lead 3   Insp.   3. Bet'n Sternum and Mid-Clav. Line

V_R   V_L   V_F   4. Mid-Clavicular Line

V_R-Insp.   V_L-Insp.   V_F-Insp.   5. Anterior Axillary Line

Fig. 4.

now inverted, and large Q waves had appeared in Leads II and III, in which Q_3 had measured 4 mm. before, and Q_2 had been negligible; the S-T and T abnormalities in Lead I remained as they had been. The record shown in Fig. 3 was made Jan. 8, 1943. The T-wave inversion in Leads II and III had receded, but the Q waves persisted, unchanged.

To be certain how large the true Q wave is, it is necessary to make the unipolar extremity leads and not depend on the standard leads entirely.
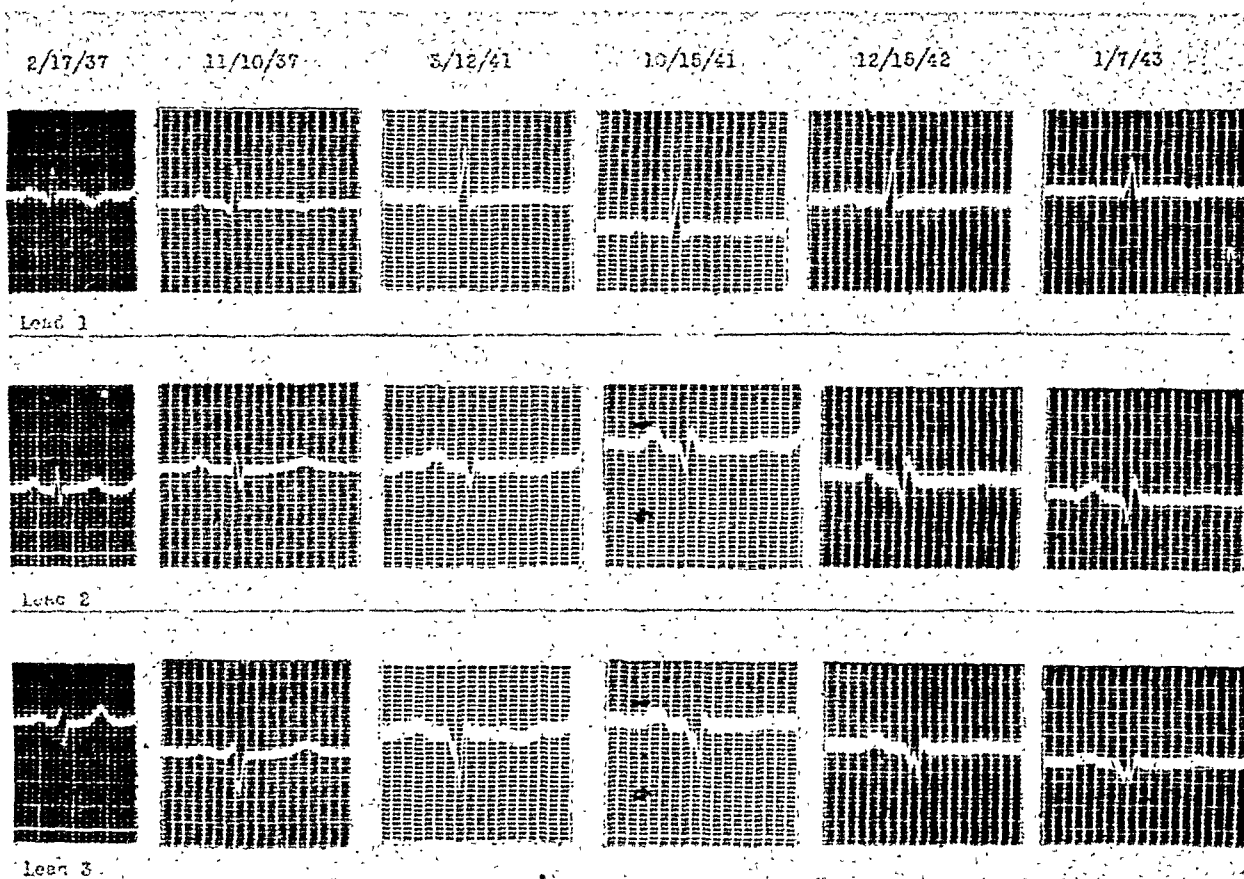
Fig. 5.

W-SHAPED COMPLEXES

Fig. 4 shows a W-shaped QRS complex in Lead III; the first limb of the W is due to a Q wave in V_F. On inspiration, the second limb of the W disappears in Lead III, while the first limb remains. The Q wave in V_F persists on inspiration and the R wave in V_L diminishes, as it did in the cases previously described.

The subject here was a man, 57 years old, who had a definite history of two coronary occlusions: the first, an anterior occlusion on Nov. 21, 1936, and the second, a posterior occlusion on Jan. 2, 1941. It is instructive to follow the changes that have taken place in the QRS complexes, as shown in Fig. 5. The Q wave in Lead III was first a slurring near the beginning of a large downward deflection, then a more definite notching, then the first limb of a W-complex.

THE PRESENCE OF R_3

Figs. 6 and 7 illustrate complexes of the QS type, with no R_3, that harbor a Q wave derived from V_F. In Fig. 6, QRS_F is monophasic and negative, with a notch on the descending limb that separates out into a clearly defined Q wave on deep inspiration. In Fig. 7, the QRS complex in V_F consists of a definite Q wave, followed by an R wave. This R wave is neutralized by the R wave in V_L, so that it appears as a terminal notch in QRS_3. Both of these subjects have, unquestionably, had coronary occlusion with typical clinical course and serial electrocardiographic changes.

THE ABSENCE OF S_3

We have several cases in which a small S_3, in a normal record taken before the occlusion, disappeared after the formation of a deep coronary Q_3. We have one such case in which a mere vestige of S_3 persisted for a short time after the formation of Q_3, and then disappeared. We have no record showing an S_3 of any magnitude in the presence of a coronary Q_3.

RIGHT AXIS DEVIATION

We have no record showing right axis deviation combined with a Q_3 which we believe to be coronary in origin.

INITIAL UPWARD DEFLECTION

A small upward deflection in Lead III, preceding the downward deflection, might arise from a QRS complex in V_F consisting of a small R wave and a large S wave, or from a small (normal) Q wave in V_L. In neither of these patterns is there any suggestion of a coronary Q wave in V_F. It is conceivable that some combination of forms might produce a small upward deflection at the beginning of QRS in Lead III with a coronary Q wave in V_F, but we have not seen such a record. On the other hand, we have seen a number of records of the two types described before. One such is shown in Fig. 8. The subject was a man, 49 years old, who was 40 pounds overweight; he had a negative history and no physical signs except a slight elevation of blood pressure.

Q_F AND Q_L AS DIAGNOSTIC SIGNS

Q waves in V_L and V_F are, unfortunately, not specific for myocardial infarction.

When the heart is vertical, the base presents about the same aspect to both arms, so that V_L looks very much like V_R. If the small upward deflection that often precedes the main downward deflection is lacking, V_L may show a large Q wave that comes through the natural orifices at the base, and not from an infarct. This is well shown in Fig. 9. The subject was a man, 25 years old, who had rheumatic heart disease, but no history suggestive of infarction.

STANDARD LEADS	PRECORDIAL LEADS

Lead 1

1. Right Sternal Border

Lead 2

2. Left Sternal Border

Lead 3   Insp.

3. Bet'n Sternum and Mid-Clav. Line

V$_R$ V$_L$ V$_F$

4. Mid-Clavicular Line

VR-Insp.   VL-Insp.   VF-Insp.

5. Anterior Axillary Line
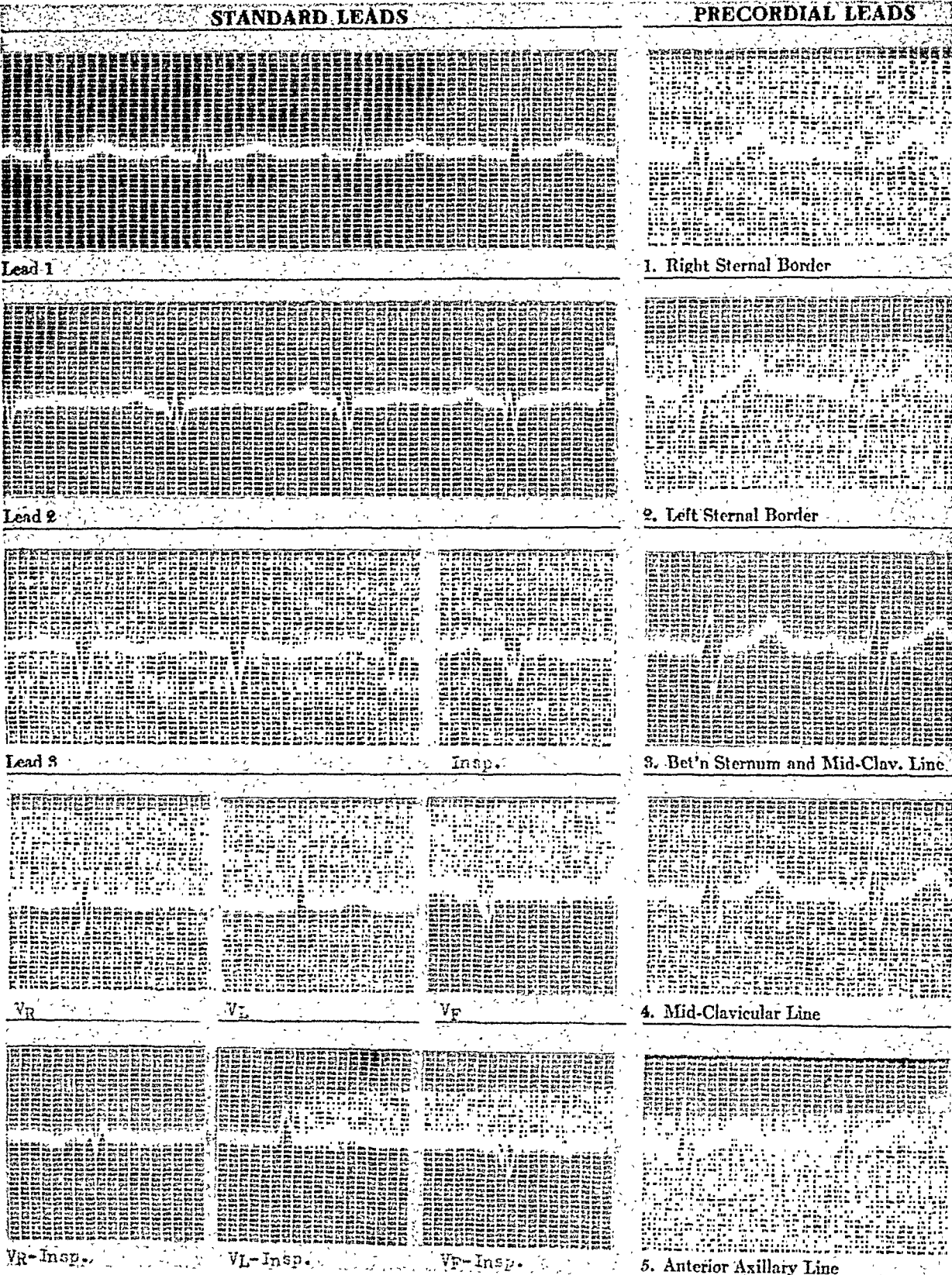
Fig. 6.

STANDARD LEADS	PRECORDIAL LEADS
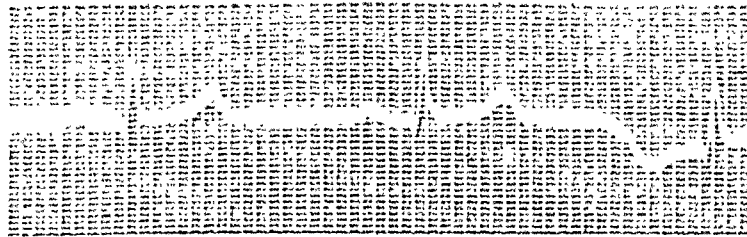
Lead 1

Lead 2
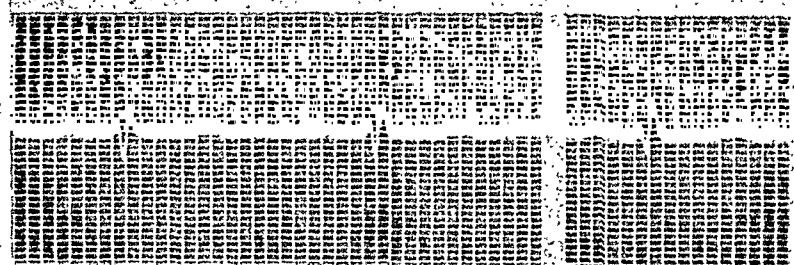
Lead 3   Insp.
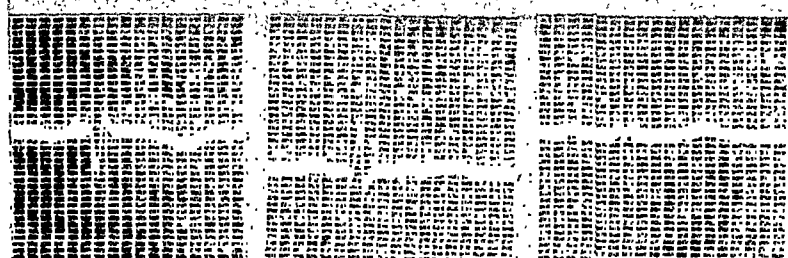
VR   VL   VF
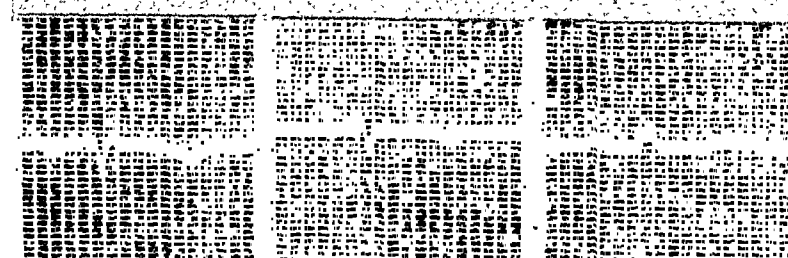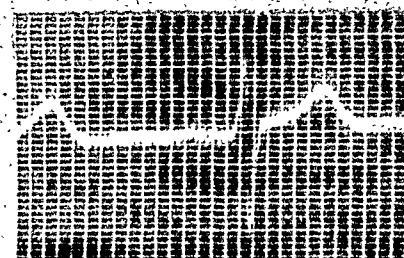
1. Right Sternal Border

2. Left Sternal Border

3. Bet'n Sternum and Mid-Clav. Line

4. Mid-Clavicular Line

5. Anterior Axillary Line

Fig. 7.

STANDARD LEADS	PRECORDIAL LEADS

Lead 1   1. Right Sternal Border

Lead 2   2. Left Sternal Border

Lead 3   Insp.   3. Bet'n Sternum and Mid-Clav. Line

V$_R$ V$_L$ V$_F$ 4. Mid-Clavicular Line

V$_R$-Insp.   V$_L$-Insp.   V$_F$-Insp.   5. Anterior Axillary Line

Fig. 8.

STANDARD LEADS	PRECORDIAL LEADS

Lead 1

1. Right Sternal Border

Lead 2

2. Left Sternal Border

Lead 3

3. Bet'n Sternum and Mid-Clav. Line

V_R V_L V_F
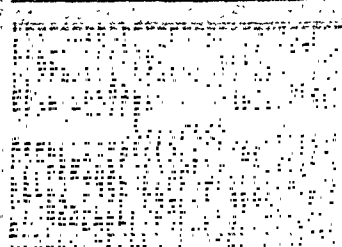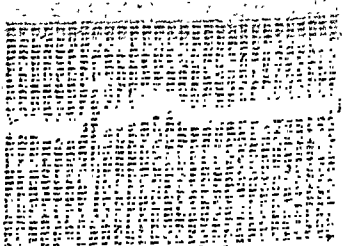
4. Mid-Clavicular Line
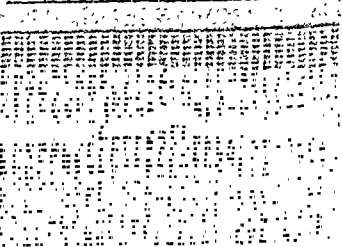
5. Anterior Axillary Line

Fig. 9.

When the heart is horizontal, it is unlikely that the tilting would be sufficient to permit the negativity of the cavity to be transmitted through the natural orifices to the foot to form a Q wave, although this might occasionally happen. What is more likely is that V_F would take the QS form, for, when the heart is horizontal, it is written by the right ventricle and so looks like V_1 and V_2, and in these the initial deflection may be very small or absent.

FREQUENCY BY COMPARISON

It is a matter of observation that a deep Q_1 is much less common than a deep Q_3. It is also known that Lead I is less subject to positional changes than Lead III.

We have, in our employee file, six deep Q_1's, as compared with twenty-nine deep Q_3's. Of those with a deep Q_3, ten have a large Q wave in V_F, and all of these have a definite history of acute occlusion. Unfortunately, only three with a deep Q_1 are available for unipolar extremity leads. Of these, two have a conspicuous Q wave in V_L, and both have had definite occlusions. (These figures do not reflect the comparative frequency of coronary and positional Q waves. It is our practice to require employees to report to the infirmary for examination after an absence of three days or more because of illness, and in this way we see all the patients with coronary occlusions that are able to return. All other examinations are purely voluntary. If we took electrocardiograms on everyone in our employ, there would be many more deep Q_3's due to position.)

A coronary Q_1 is shown in Fig. 10. The subject was a man, 36 years of age, who had an unmistakable coronary occlusion at the age of 31 years. The diagnosis was based on a typical clinical course and confirmed by characteristic serial changes in the electrocardiograms during the acute period. He has a definite Q wave, of unusual width, in V_L.

Fig. 11 shows a Q_1 which, although contributed to by a small Q wave in V_L, is due mainly to an initial upward deflection of the QRS complex in V_R. The subject was a woman, 53 years of age. She had complained of mild precordial pain and dyspnea for some months, but she had had no acute attack. Our observations on unipolar extremity leads are not extensive enough for us to say whether an R wave of this amplitude in V_R is abnormal or not, but the Q in Lead I is not the Q wave of infarction.

It is interesting that the Q_1's in our file which satisfy the "infarction test," that is, those associated with Q_L, are much less frequent than the Q_3's associated with Q_F, although the anterior and posterior occlusions in this file are equally divided, i.e., sixteen anterior and sixteen posterior. A little reflection reveals why this may be so. The heart presents a broad posterior surface to the foot, so that any posterior infarction that produces a Q wave will make the Q wave show in V_F, regardless of minor variations in its location. But an anterior infarct will not produce QRS changes in Lead I unless the central portion of the in-

STANDARD LEADS | PRECORDIAL LEADS
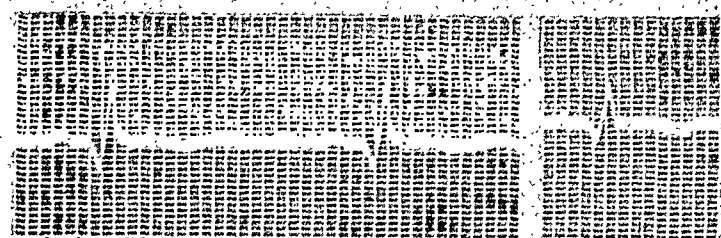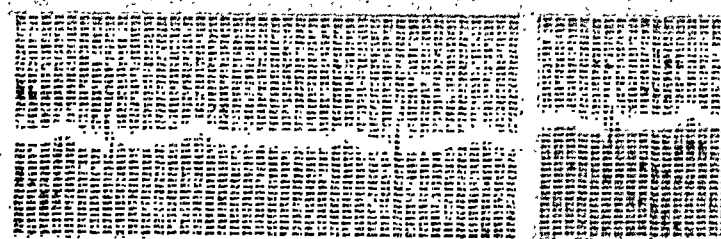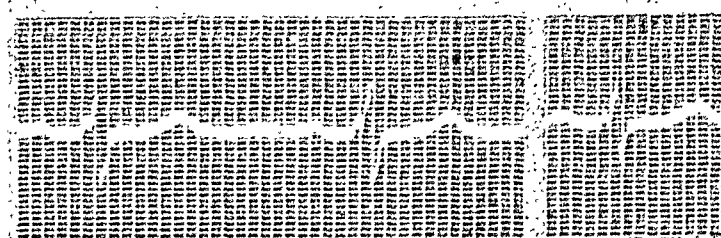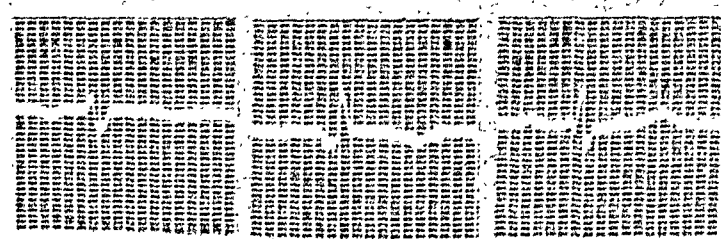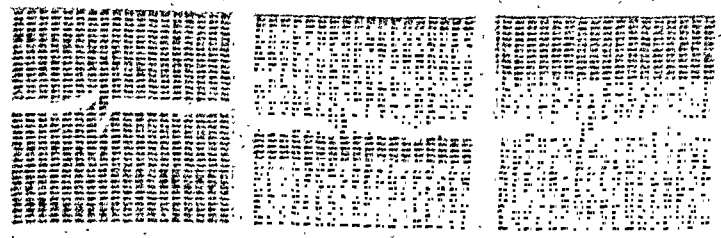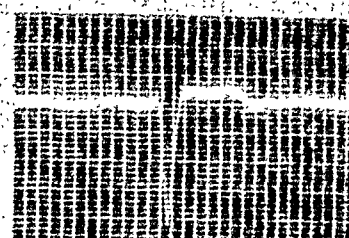
Lead 1   Insp.   1. Right Sternal Border

Lead 2   Insp.   2. Left Sternal Border

Lead 3   Insp.   3. Bet'n Sternum and Mid-Clav. Line

                                                   4. Mid-Clavicular Line

                                                   5. Anterior Axillary Line

Fig. 10.

STANDARD LEADS	PRECORDIAL LEADS
Lead 1	1. Right Sternal Border
Lead 2	2. Left Sternal Border
Lead 3	3. Bet'n Sternum and Mid-Clav. Line
V$_R$ V$_L$ V$_F$	4. Mid-Clavicular Line
	5. Anterior Axillary Line
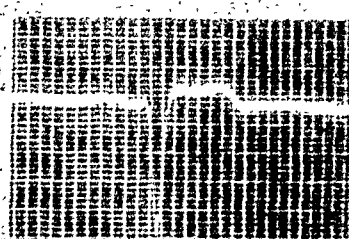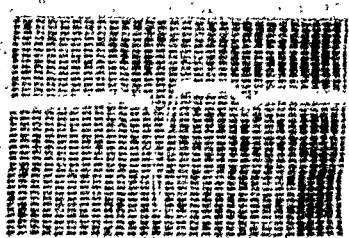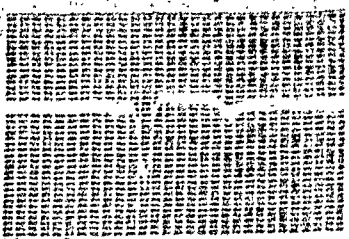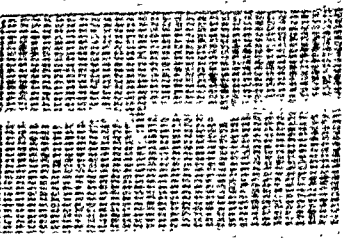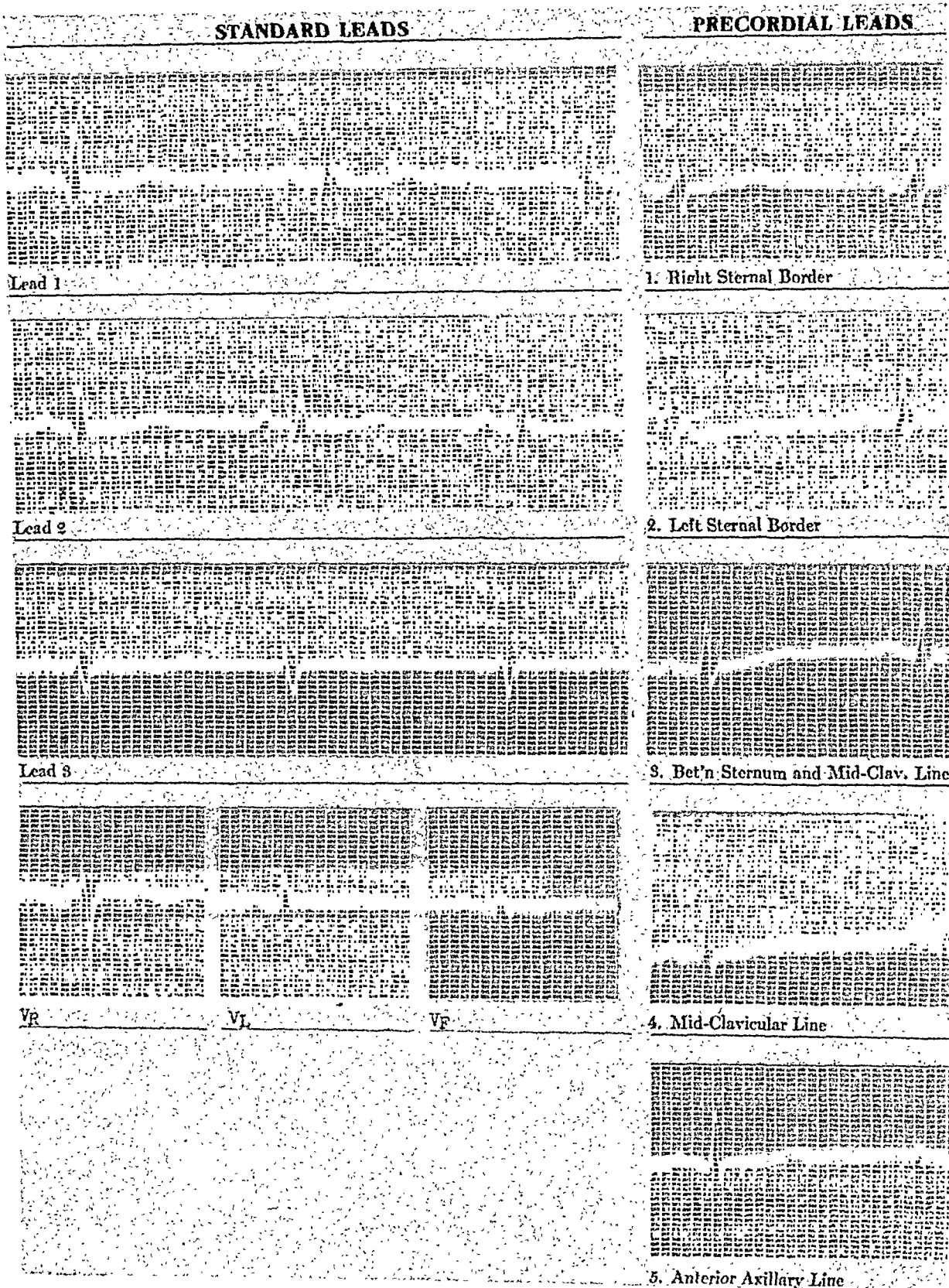
Fig. 11.

farcted area is on the lateral or anterolateral aspect of the ventricle; an anteroseptal infarct produces QRS changes, usually, in precordial leads from positions 2 and 3, although the marginal portions of the infarcted area may extend far enough to the left to produce T-wave inversion in Lead I without QRS changes.

In our experience, only a small proportion of the deep Q_2's are of coronary origin.

SUMMARY

Working on the theory that a Q wave in Lead III produced by infarction is due to a Q wave in V_F, the author has drawn the following tentative conclusions:

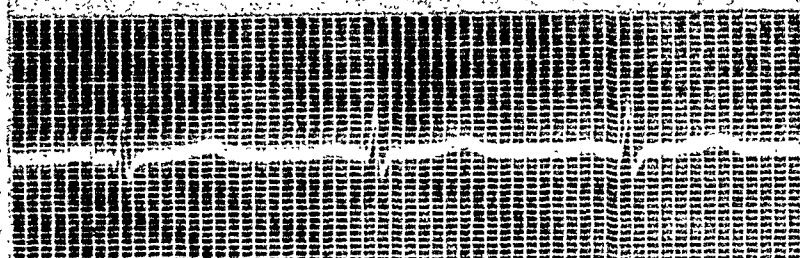1. The disappearance of Q_3 on deep inspiration is probably proof that it is positional, although failure to disappear is not incontrovertible proof of a coronary origin.

2. The voltage of Q_2 is a fairly good index of the depth of the Q wave in V_F, but this is not absolutely dependable.

3. A significantly deep Q_2 may be less than 25 per cent as large as the largest R wave.

4. W-shaped QRS complexes in Lead III may contain a deep Q_3.

5. R_3 need not be present.

6. A small, initial, upward deflection apparently takes the Q_3 out of the coronary class.

7. A deep Q_3 that is due to infarction is relatively rare.

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THE PERIPHERAL BLOOD FLOW AND OTHER OBSERVATIONS IN COARCTATION OF THE AORTA

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COARCTATION of the aorta is a congenital constriction of the aorta, usually in the region of the insertion of the ductus arteriosus. The degree of constriction varies from slight narrowing to complete atresia. The important diagnostic features are elevation of blood pressure in the arms, with the blood pressure in the legs low or unobtainable, and evidences of collateral circulation. Palpable and visible pulsations, with an accompanying bruit, over the intercostal arteries, and roentgenologic evidence of erosion of the lower rib margins are evidences of collateral circulation. The pulsations in the femoral, popliteal, and dorsalis pedis arteries are small or absent.

There have been a few studies of the circulation in this congenital anomaly. In 1933, Lewis,[1] using the plethysmographic method of Hewlett and Zwaluwenberg, found that the blood flow in the legs of patients with coarctation of the aorta was normal or slightly increased. Pickering,[2] in a study of several types of hypertension, found that the blood flow in the arms was normal in coarctation of the aorta, and that there was a normal response to reactive hyperemia. Stewart and Bailey's observations[3] showed that the cardiac output per minute was normal or increased in all except one of nine cases. The average minute volume output was 2.6 1./sq. m./min., compared to 2.2 1./sq. m./min. for normal persons. Blumgart, Lawrence, and Ernstene[4] found normal arteriolar pressure in the arms, lowered oxygen saturation of the femoral arterial blood, a normal arteriovenous oxygen difference in the legs, and blood plasma volume near the upper limit of normal. Friedman, Selzer, and Rosenblum[5] found that there was partial renal ischemia. This was compensated, however, by increased intraglomerular pressure, which caused a normal rate of glomerular filtration. There have been attempts[6, 7] to relate the hypertension of coarctation of the aorta to the Goldblatt type of hypertension.

In the present investigation, data have been compiled relating to the amount of blood allotted to the peripheral circulation in coarctation of the aorta. The peripheral blood flow was measured in twelve patients with coarctation and compared with similar measurements in twenty-

four normal male subjects.[6] Skin temperatures at eleven locations on the body surface and rectal temperatures have been compared with the temperature of these areas in normal subjects.

METHODS

The peripheral blood flow was measured by a modification of the method of Hardy and Soderstrom,[9] in which blood flow is expressed as a function of heat loss, surface area, average skin temperature. and rectal temperature. In order to use this method, certain data were required, namely, measurement of skin and of rectal temperature, oxygen consumption, and body weight and height. The oxygen consumption was measured with a Benedict-Roth apparatus,[10] and surface area and basal metabolic rates were calculated from the tables of Dubois and Dubois[11] and the Boothby, Barkson, and Dunn normogram for age and sex.[12] The skin temperature was measured with the improved Hardy-Soderstrom radiometer,[13] and the rectal temperature with a single junction copperconstantan thermocouple. The locations of the eleven areas on the body surface at which readings of skin temperature were taken are shown in Fig. 1. The formulae for calculation of peripheral blood flow from the above data have been presented in previous studies by Stewart and Evans[14] and Stewart and Jack.[15] Three to seven sets of skin and rectal temperatures were made at ten- to twenty-five-minute intervals, from which average peripheral blood flows were calculated. Since heat storage was calculated on the basis of one hour, a suitable time factor[14] provided for the variation in the time intervals.

PLAN OF PROCEDURE

All observations were made in the morning with the subjects under basal conditions, in a room in which the temperature was maintained constant within $0.5°$ C. All studies were made at $25°$ C., and, in Case 4, observations were also made at $26°$ C. The humidity of the room during observations relating to Cases 1, 3, 4, 5, 6, and 8 was kept at approximately 40 per cent, and, in the others, was not estimated. Before observations were begun, the subjects were kept at rest for an hour, for adjustment to room temperature, and care was taken to prevent apprehension or other emotional disturbance.

The blood pressure in the right arm and the pulse rate were taken after each set of eleven skin temperature readings. After obtaining the last basal metabolic rate, the blood pressure was measured in all four extremities, after which an electrocardiogram was taken. A teleoroentgenogram of the heart was then taken for calculation of the cardiothoracic ratio and to see whether there was erosion of the ribs.

The arm-to-tongue circulation time was measured with decholin[16] in four subjects, and the circulation time from arm to throat, perineum. and all four extremities with macasol[17] in five subjects. Carotid sinus time[18] was used in three subjects.

OBSERVATIONS

Peripheral Blood Flow.—The peripheral blood flow in thirteen observations on twelve subjects ranged from 14 to 129 c.c./sq. m./min.; the average for the group was 68 c.c./sq. m./min. (Table I, Fig. 1). The range was somewhat greater and the average higher than in the normal
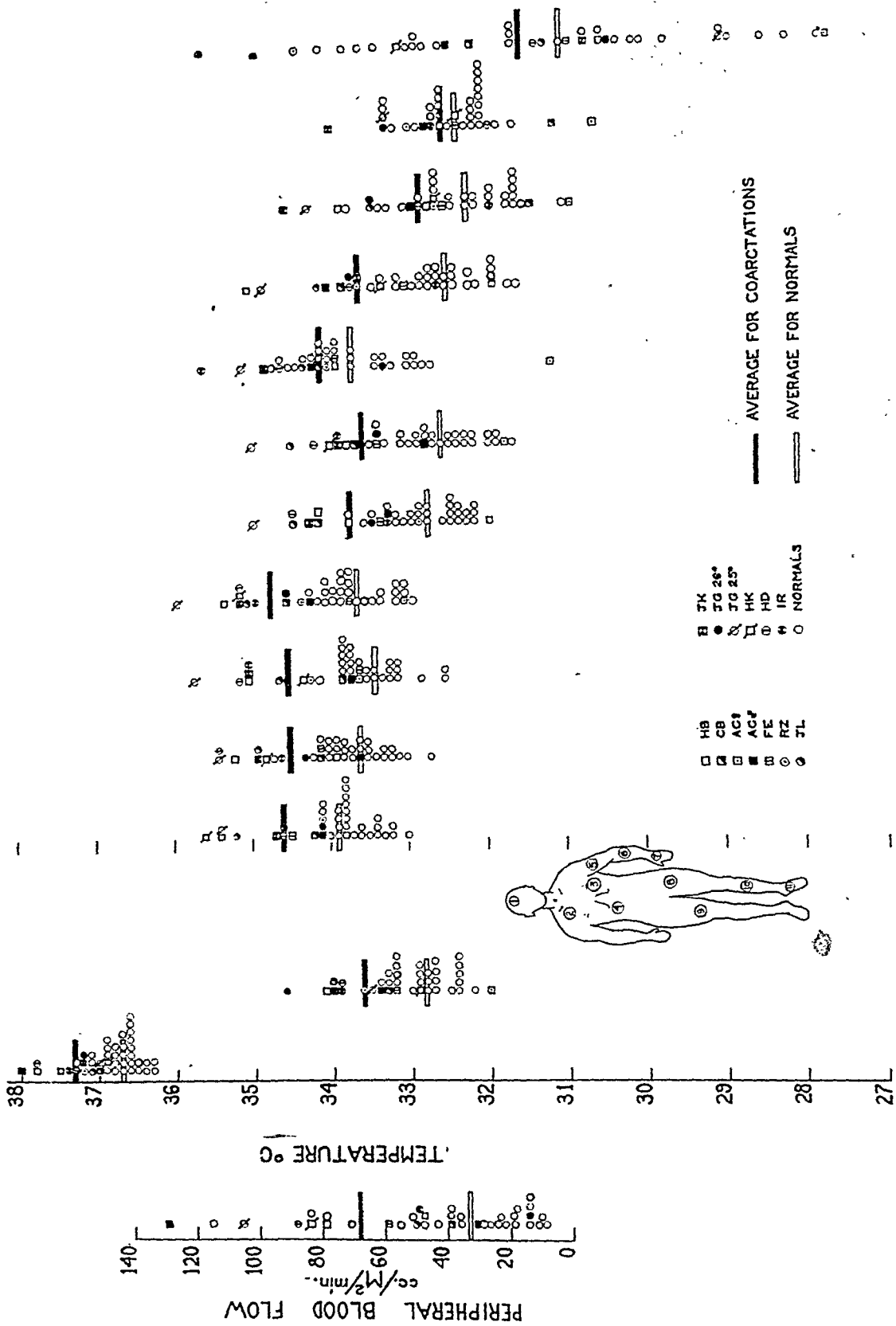
Fig. 1.—In this figure are shown, for each subject, the average peripheral blood flow, rectal temperature, average weighted skin temperature, and skin temperature at eleven areas on the anterior surface of the body. The location of these eleven areas is indicated. Each patient with coarctation of the aorta is represented by a different symbol, and all members of the areas is indicated. Each patient with coarctation of the aorta is represented by a different symbol, and all members of the normal control group by the same symbol. The solid black and the open rectangle indicate the averages for each group, respectively. In each instance, the value is higher in the coarctation group than in the normal controls.

TABLE 1

PERIPHERAL BLOOD FLOW, SKIN AND RECTAL TEMPERATURES, AND BASAL METABOLIC RATES IN TWELVE PATIENTS WITH COARCTATION OF THE AORTA

NAME, CASE NUMBER, HISTORY NUMBER	DATE	PERIPHERAL BLOOD FLOW (C.C./SQ. M./MIN.)	BASAL META-BOLIC RATE (%)	AVERAGE RECTAL TEMPERA-TURE (°C.)	AVERAGE WEIGHTED SKIN TEMPERATURE (°C.)	SKIN TEMPERATURE OF AREAS OF BODY (°C.)											PULSE RATE (PER MIN.)
						1	2	3	4	5	6	7	8	9	10	11	
J. R. Case 1 227208	3/3/39	48	-5	37.43	33.91	34.6	34.6	35.0	34.9	33.2	33.8	33.5	32.5	31.8	32.5	35.4	
H. D. Case 2 96890	2/23/43	87	+6	37.85	33.91	34.6	35.4	35.1	35.1	34.4	34.1	34.5	33.6	32.7	31.8	31.2	70
H. K. Case 3 286038	1/24/40	83	-4	36.87	33.85	35.6	34.8	34.3	35.1	34.1	33.9	34.0	33.2	32.5	32.3	32.9	80
J. G. Case 4 204008	3/16/39 25°	106	-21	37.18	34.55	35.4	35.4	35.7	35.9	34.9	34.9	35.0	34.7	34.1	33.1	28.9	64
	6/4/42 26°	14	-18	36.94	33.53	34.1	34.3	34.5	34.5	33.4	33.3	33.2	33.6	33.3	33.1	30.3	76
J. K. Case 5	11/14/41	129	+11	37.24	34.12	34.7	34.9	35.0	35.1	34.2	33.8	34.7	33.5	34.4	33.8	30.6	80

	Date																
J.L. Case 6 260384	3/20/40	50	-11	37.11	33.97	35.2	34.9	34.6	35.0	34.4	34.4	34.2	34.0	33.3	32.4	31.1	76
R.Z. Case 7 254257	8/ 5/42	115	-15	37.21	33.55	34.1	33.5	34.2	34.3	32.8	33.2	33.9	33.5	32.5	32.8	34.2	72
F.E. Case 8 331019	6/30/43	59	+13	37.30	33.16	34.5	34.1	33.6	33.7	33.3	33.3	33.8	32.9	32.4	32.3	30.8	77
A.C. Case 9 256260	11/23/42	33	-7	37.95	33.38	34.1	33.6	33.7	34.2	33.2	32.7	34.1	33.9	32.8	32.0	32.3	68
A.C. Case 10 237888	8/24/42	47	-11	37.84	31.95	33.8	33.9	33.6	33.0	31.9	31.7	31.1	31.7	30.8	30.5	27.6	67
C.B. Case 11 304713	8/ 8/42	39	-17	36.97	33.25	34.2	34.1	33.8	34.5	34.1	33.6	34.0	33.7	31.3	31.0	32.0	55
H.B. Case 12 338907	10/24/42	78	+4	37.46	34.08	35.4	35.2	35.0	35.3	33.7	33.7	33.8	34.9	33.7	32.4	30.4	105
Average for Group		68	-6	37.33	33.63	34.64	34.52	34.47	34.66	33.66	33.57	33.98	33.52	32.74	32.35	31.36	

subjects studied by Stewart and Evans,* whose range at the same temperature was from 8 to 84 c.c./sq. m./min., and the average, 33 c.c./sq. m./min. (Table II, Fig. 1).

Rectal Temperature.—The average of the rectal temperatures for subjects with coarctation was 37.33° C., 0.61° C. higher than for the normal group, in which it was 36.72° C. (Tables I and II, Fig. 1).

Average Skin Temperature.—The average of the weighted skin temperatures for the twelve subjects with coarctation was 33.63° C., compared to 32.82° C. for the normal group; in short, it was 0.81° C. higher. The trend was similar to the rectal temperatures (Tables I and II, Fig. 1).

Skin Temperature of the Eleven Body Areas.—Marked deviation from the normal occurred in the temperature of the eleven selected points on the body surface (Fig. 1). The readings at each point for the twelve subjects showed considerable variation from case to case, but the skin temperatures of corresponding locations on normal persons showed less spread.

The average of the temperatures for each of the first nine points, corresponding roughly to the upper part of the body, including the thighs, was much higher for the subjects with coarctation than for the normal subjects. The average of forehead temperatures in the coarctation patients was 34.64° C., compared to 33.92° C. for the normal; the subclavian area, 34.52° C., compared to 33.66° C.; under the left breast, 34.47° C., compared to 33.44° C., right hypochondrium, 34.66° C., compared to 33.59° C.; left upper arm, 33.66° C., compared to 32.67° C.; left forearm, 33.57° C., compared to 32.45° C.; left hand, 33.98° C., compared to 33.59° C.; left upper thigh, 33.52° C., compared to 32.39° C.; right lower thigh, 32.74° C., compared to 32.11° C. For the other two points the difference was less; the left leg was 32.35° C. in coarctation, compared to 32.22° C., and the dorsum of the left foot, 31.36° C., compared to 30.91° C. (Tables I and II, Fig. 1).

The three points, therefore, where the temperature difference between the two groups was least were the left hand, left leg, and dorsum of the left foot, with differences of 0.39° C., 0.13° C., and 0.45° C., respectively. At the last point measured, there was a wide range of variation in the coarctation as well as normal group; the range was from 27.6° C. to 35.4° C. in the former, and 27.1° C. to 33.9° C. in the latter.

Basal Metabolic Rate.—The basal metabolic rate in the subjects of this investigation varied from –21 per cent to +13 per cent, with an average of –6 per cent (Table I). The average was not significantly different from that of –3 per cent in the group of the twenty-four normal persons whose range was –19 per cent to +31 per cent.

Circulation Time.—Circulation time was measured with macasol in seven subjects. In Case 2, a child of 11 years, the circulation time to the tongue, perineum, right hand, and both feet was, perhaps, slightly decreased below the average for a child his age, and an end point was

not obtained in the perineum and left hand (Fig. 2). In Case 5, a boy of 15 years, end points were obtained at all areas, and the decreases below the average figure were approximately of the same magnitude as in Case 2. In Case 12, the circulation time was considerably below the average value; an end point was not detected in the left hand. In
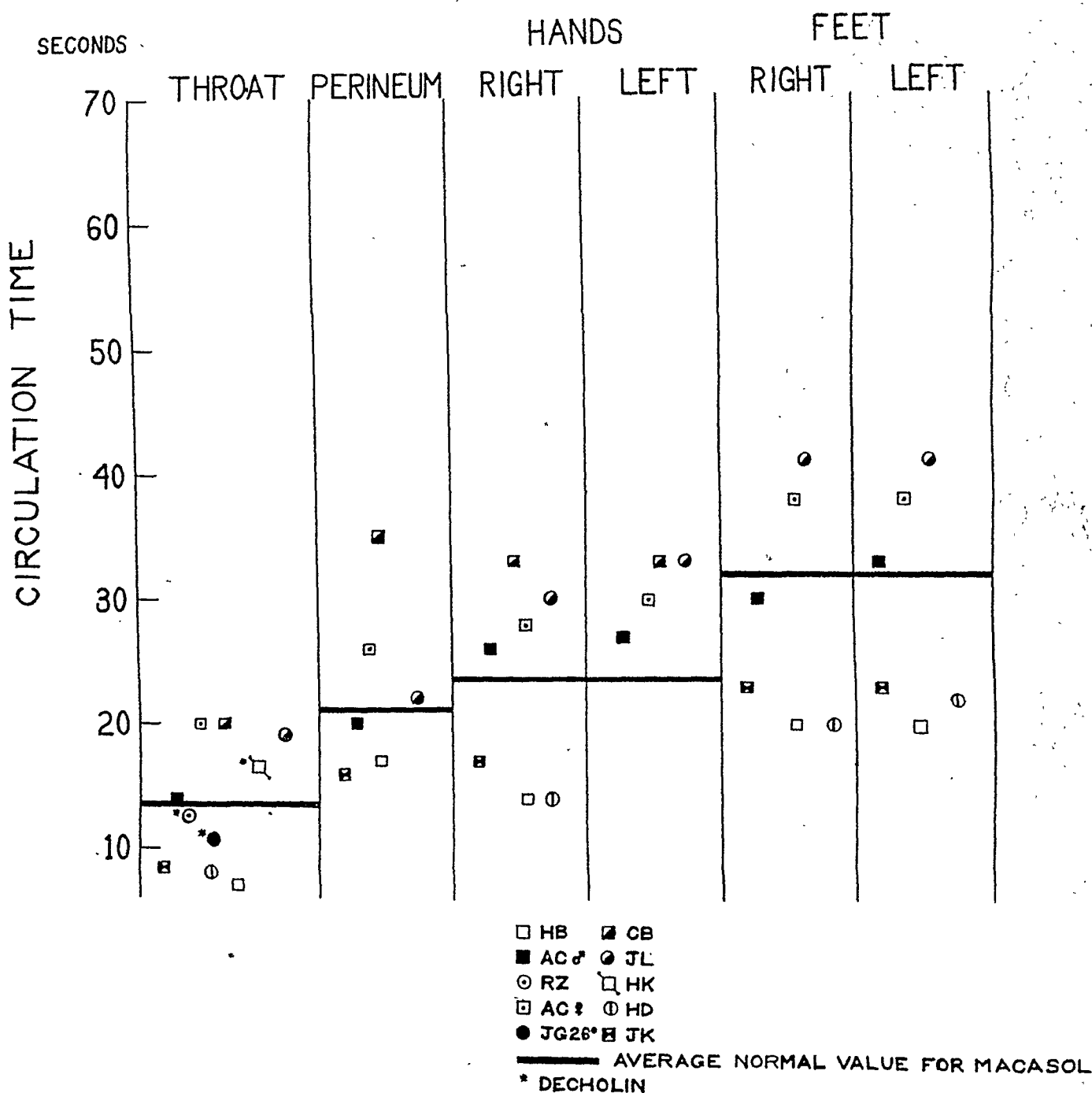
Fig. 2.—In this figure are recorded circulation times of subjects with coarctation of the aorta. In those marked with an asterisk, decholin was used as the testing substance; in all others macasol was used. The horizontal lines show the average values for normal persons.

Case 9, the circulation times were very close to the average normal figure, and, in Cases 6, 10, and 11, it was moderately prolonged; in the latter case, end points were not elicited in the feet.

In the three cases in which decholin was used as the test substance, the circulation time was prolonged slightly above the average in one

TABLE II

Peripheral Blood Flow, Skin and Rectal Temperatures, and Basal Metabolic Rate in Twenty-Four Normal Subjects (Stewart and Evans)[8]

NAME	DATE	PERIPHERAL BLOOD FLOW C.C./SQ. M./MIN.	BASAL METABOLIC RATE (%)	AVERAGE RECTAL TEMPERATURE (°C.)	AVERAGE WEIGHTED SKIN TEMPERATURE (°C.)	SKIN TEMPERATURE OF AREAS OF BODY (°C.)										
						1	2	3	4	5	6	7	8	9	10	11
K.D.	7/25/41	43	-5	36.62	33.22	33.8	33.8	33.8	33.9	33.2	33.0	34.0	32.6	32.7	31.7	33.2
J.F.	7/17/41	24	-2	36.84	32.79	33.9	33.7	33.7	33.8	33.1	31.8	32.8	33.0	31.8	31.9	30.0
A.R.	6/12/41	47	+3	36.82	33.21	33.9	34.7	33.7	34.0	33.2	33.4	33.8	33.2	32.3	32.4	29.9
G.D.	7/5/41	14	-7	36.71	32.86	33.7	33.8	33.2	33.0	32.7	32.4	34.4	31.8	31.8	32.4	32.7
W.McD.	6/28/41	55	-1	36.65	33.23	33.5	33.2	33.5	33.9	32.4	32.2	34.6	32.1	33.6	33.1	33.4
R.T.	6/10/41	23	-13	36.49	32.19	33.6	32.7	32.8	33.1	32.4	32.3	32.9	31.6	31.6	32.0	28.9
T.L.	7/19/41	75	+11	36.76	33.32	34.1	33.9	33.8	33.8	32.7	32.8	34.0	33.0	32.3	33.1	32.8
S.H.	7/15/41	51	+31	36.72	32.40	33.0	33.2	33.2	33.0	32.1	32.4	32.9	32.0	31.4	32.0	30.6
A.M.	7/16/41	28	-11	36.77	32.41	33.3	33.0	32.5	33.1	32.4	31.9	33.1	31.8	32.0	32.0	31.5
J.B.	7/20/41	26	-7	36.37	32.39	33.7	33.3	32.5	32.9	32.3	32.7	33.6	31.8	31.6	32.1	30.2
T.R.	7/12/41	11	-17	36.60	32.71	33.4	33.5	33.1	33.4	32.7	32.7	33.9	32.3	31.5	31.9	31.9
C.H.	7/11/41	18	-12	36.63	32.89	33.5	35.3	33.2	33.1	32.1	32.6	33.8	32.6	32.5	32.5	32.6
R.O.	7/21/41	37	+8	36.66	32.92	33.4	34.0	33.7	33.8	33.1	32.9	34.2	32.4	30.9	31.9	32.4
G.L.	7/10/41	10	-1	37.06	32.68	33.5	34.2	33.1	33.3	32.8	31.9	32.8	32.4	32.5	32.7	28.1
A.P.	7/9/41	14	-4	37.07	32.53	33.8	34.0	33.5	34.1	32.2	31.8	32.8	32.7	31.5	31.9	27.1
F.McN.	6/27/41	8	-18	36.87	32.43	33.8	33.1	33.5	34.0	32.4	32.2	33.6	31.5	31.5	31.9	28.8
R.M.	6/26/41	19	-19	36.58	32.74	33.9	33.6	33.6	33.7	32.2	32.1	32.7	32.3	32.1	32.0	30.9
J.S.	6/24/41	18	-8	36.42	32.75	33.8	33.5	33.4	33.3	32.9	32.5	33.9	32.1	31.5	31.9	31.5
L.L.	6/23/41	38	-10	36.85	33.26	34.0	33.6	33.3	33.7	33.0	33.0	34.5	32.5	32.9	32.4	33.6
F.E.	6/21/41	22	+16	37.26	32.84	33.8	34.0	34.1	34.2	33.5	32.3	33.3	32.5	32.0	31.9	28.4
J.S.	6/18/41	14	-10	36.60	32.41	34.0	33.9	33.8	33.8	32.3	31.6	32.6	32.3	31.5	31.9	27.7
B.V.	6/11/41	71	+4	36.53	32.98	35.8	33.4	33.1	33.8	32.7	32.8	34.1	32.7	32.5	33.0	33.9
C.S.	6/30/41	39	+1	36.90	33.39	33.9	33.7	33.8	34.0	32.3	32.1	33.3	33.3	33.2	32.3	29.6
L.E.	7/29/41	84	+7	36.55	32.72	33.8	34.1	33.7	33.7	33.4	33.3	34.3	32.8	32.1	32.5	32.7
	6/20/41	36	-3	36.73		33.2	33.8	33.4	33.6	32.5	32.6	33.6	32.6		31.5	30.4
Average for Group		33	-3	36.72	32.82	33.92	33.66	33.44	33.59	32.67	32.45	33.59	32.39	32.11	32.22	30.91

(Case 3), decreased below the average in one (Case 4), and, in one (Case 7), it was within normal limits. In two patients (Cases 4 and 6), the CO_2 time (lung to carotid sinus) was decreased, and, in one (Case 3), it was prolonged.

Electrocardiographic Changes.—Electrocardiograms were taken in all but Case 5. Of the nine subjects still living who had electrocardiograms, three had essentially normal electrocardiograms without axis deviation (Cases 2, 6, and 12), one (Case 11) had right axis deviation with a diphasic T_2, T_3, and T_4, and five had left axis deviation (Cases 4, 7, 8, 9, and 10), together with negativity of the T waves in Lead III (Table III).

Both of the patients who died (Cases 1 and 3) had left axis deviation; in Case 1 there were negativity and coving of the T waves in all leads, and, in Case 3, there were negativity and slight coving of the T waves in Lead I, and, later, negativity of the T waves in Lead II, as well. In short, these patients differed from those still living in that they had changes in the T waves in Lead I, whereas those surviving had alterations in Lead III. In these two cases, post-mortem examination revealed moderate atherosclerosis of the coronary vessels. In Case 1, there was evidence in microscopic sections of progressive degeneration of the heart muscle, with diffuse atrophy of the fibers and vacuolization, presumably edema, in some areas, and moderately advanced fibrosis in other areas. In Case 3, there were focal areas of diffuse myocardial fibrosis, with more extensive scarring; yellow pigment, probably hemosiderin, was present, no doubt indicating preexisting hemorrhage at these sites.*

Cardiac Size.—Teleoroentgenograms were available for measurement in all but Cases 1 and 5. An increase in the cardiothoracic ratio, indicating cardiac enlargement, was present in only two subjects (Cases 7 and 8) (Table III), but was demonstrated at autopsy in Cases 1 and 3. In this group, there was apparently no common factor, such as age or level of blood pressure, to correlate with the enlargement.

Evidence of Collateral Circulation.—One or more signs of collateral circulation were present in all except Case 10 (Table III). These were not sought in Case 1, in which the constriction was minimal and the diagnosis of coarctation was made at autopsy. Intercostal pulsations, a bruit over the intercostal arteries, and scalloping of the rib margins in the roentgenograms were present in Cases 2, 4, 6, 7, 8, 9, 11, and 12; pulsations without a bruit, but with scalloping, were evident in Case 3, and none of these signs were detected in Case 10.

DISCUSSION

These studies show that the average peripheral blood flow is greater in coarctation of the aorta than in normal persons; that is to say, the average amount of blood allotted to the body surface from the total

TABLE

SUMMARY OF THE CLINICAL DATA OF TWELVE

CASE NUMBER, NAME, AGE, SEX	DURA-TION OF SYMP-TOMS	AGE AT WHICH DIAG-NOSIS WAS MADE (YEARS)	SYMPTOMS							BLOOD	
			DYSP-NEA	EDE-MA	FA-TIGUE	PAL-PITA-TIONS	PRE-COR-DIAL PAIN	CLAU-DICA-TION	HEAD-ACHE	RIGHT ARM	LEFT ARM
1. I. R.* 48 ♀	6 yr.	at autopsy	+	÷	+	0	+	0	+	255/160	240/160
2. H. D. 11 ♂		11	+	0	0	0	0	0	0	140/70	140/60
3. H. K.† 64 ♂	1 yr.	64	+	0	+	0	0	0	0	172/90	170/90
4. J. G. 15 ♂ 19	3 wk.	15	0	0	0	+	0	0	0	150/80 150/60	150/80 140/70
5. J. K. 13 ♂										160/110	164/114
6. J. L. 23 ♂	3 yr.	22	÷	0	+	÷	+	0	÷	160/86	144/80
7. R. Z. 30 ♀		27	0	0	↑0	0	0	0	0	180/116	198/116
8. F. E. 37 ♂		37	0	0	0	0	0	0	0	200/110	196/106
9. A. C. 20 ♂	8 yr.	17	÷	0	0	÷	0	÷	0	174/98	160/112
10. A. C. 41 ♀	7 yr.	38	0	0	0	÷	÷	0	0	170/110	162/92
11. C. B. 35 ♂	1½ yr.	34	0	0	0	0	÷	0	0	190/110	190/110
12. H. B. 21 ♂	1 yr.	21	÷	0	0	0	0	0	0	162/92	156/94

*Dissecting aneurysm of arch of the aorta, aortic insufficiency and aortic stenosis, only mild arteriosclerosis of coronary arteries, slight constriction of aorta just below origin of left subclavian. Heart weight = 470 grams. Hypertrophy and dilatation of heart.

†Coarctation in region of entrance of ductus arteriosus, moderate arteriosclerosis of coronary arteries. Dilatation of innominate, left carotid, left subclavian, internal mammary, intercostal, and epigastric arteries, and costocervical trunk. Heart weight = 600 grams. Hypertrophy and dilatation of heart. Carcinoma of larynx, with metastases and terminal B. hemolytic streptococcus septicemia.

‡L.A.D. = Left axis deviation.
§R.A.D. = Right axis deviation.
¶X-ray not available for examination.
∼Not examined for this.

cardiac output is increased. The range from one case to the other was also somewhat greater than in normal subjects. There was overlapping in the normal and coarctation values, which was not unexpected, for,

III

PATIENTS WITH COARCTATION OF THE AORTA

PRESSURE		PULSATIONS IN ARTERIES			EVIDENCE OF COLLATERAL CIRCULATION			CARDIO-THORACIC RATIO	AORTIC INSUFFICIENCY	SYSTOLIC MURMUR	ELECTRO-CARDIOGRAM
RIGHT LEG	LEFT LEG	FEMORAL	POPLITEAL	DORSALIS PEDIS	INTERCOSTAL PULSATIONS	BRUIT	SCALLOPING OF RIBS IN X-RAY				
	290/200	present	present	present	¶	¶	‖		+	+	L.A.D.,‡ negativity and coving of T waves in all leads
90/80	95/90	faint	absent	absent	+	+	+	0.44	+	+	Essentially normal. Marked sinus irregularity. T_3 diphasic
115/110	100	absent	absent	absent	+	0	+	0.46	0	0	L.A.D. T_1 first slightly coved and then T_1 and $_2$ became negative
95/85 90/80	90/80 100/80	small	absent	absent	+	+	+	0.40	0	+	L.A.D. Sinus irregularity. T_3 diphasic
not obtained	not obtained										
110/80	108/80	small	absent	small	+	+	+	0.45	0	+	Essentially normal
not obtained	112/110	absent	absent	absent	+	+	+	0.53	0	+	L.A.D. T_3 negative in some and upright in others
130/110	130/110	faint	absent	absent	+	+	+	0.54	0	+	L.A.D. T_3 diphasic
130/110	120/110	small	absent	absent	+	+	+	0.44	0	+	L.A.D. Sinus irregularity. T_3 negative and coved
not obtained	98/70	small	absent	absent	0	0	0	0.51	0	+	L.A.D. $T_{2, 3,}$ and $_4$ diphasic
138/110	116/98	small	absent	small	+	+	+	0.43	0	+	R.A.D.§ $T_{2, 3,}$ and $_4$ diphasic
125/100	125/90	small	small	small	+	+	+	0.41	0	+	Essentially normal

in normal subjects, variations are known to occur from day to day in the same subject under the same environmental conditions.[6] Therefore, even though in individual instances of coarctation the peripheral blood flow may be lower than in certain normal persons, the average for the group is greater than the average for the normal group.

The increase in blood flow to the periphery was paralleled by an increase in internal body temperature; the average rectal temperature was 0.61° C. higher than in normal subjects. Furthermore, in only five of the twenty-four normal subjects was the rectal temperature as high as the lowest temperatures recorded in subjects with coarctation.

When peripheral blood flows were plotted against rectal temperatures, it was seen that the increase in the coarctation group was not due to the increased internal temperature. The average of the weighted skin temperatures showed the same trend as the rectal temperatures, namely, higher than in normal subjects. The increase in blood flow to the periphery accounts for the rise in the average skin temperatures of these patients. The averages for each of the eleven areas from which temperatures were derived were greater in the coarctation group than in the normal subjects. The deviation from normal values was less in the hands, the lower part of the leg, and the foot.

The cardiac output per minute in coarctation of the aorta is, in most instances, increased,[3] so that there is available the increased amount of blood which is allotted to the periphery of the body. The peripheral blood flow method which was used measures the average amount of blood allotted to the periphery of the whole body; the amount allotted to the upper part of the body may be increased and that to the lower part may be diminished in some cases, and yet the average for the whole body may be greater than normal. Lewis,[1] however, found that the amount of blood allotted to the legs was normal or slightly increased; moreover, the increased local temperature of these parts in the cases now being reported was additional evidence that the circulation was not impaired. Friedman, Selzer, and Rosenblum[5] found decreased renal blood flow in cases of coarctation. This observation was based upon the reduction in diodrast clearance, which apparently did not interfere with renal function, for the rate of glomerular filtration (measured by inulin clearance) was normal. Studies are not available concerning blood flow to other portions of the body of persons with this congenital defect.

The circulation time was prolonged in some subjects, decreased in others, and normal in others. The prolongation of the circulation time is probably indicative of the devious route by which the blood reached the various parts of the body by way of the collateral arterial channels in these subjects. Those whose circulation time was shortened may have been those whose cardiac output was sufficiently increased to overcome the increase in vascular bed. Two subjects whose circulation time was shortened were young people, in whom the velocity of blood flow may be normally shorter and the cardiac output greater than in adults.[19] Moreover, if their cardiac output was still greater than would be expected in normal youths, this would have been added reason for the shortened circulation time.

Certain observers[20-22] have found that the basal metabolic rate may be elevated in coarctation of the aorta. It is recalled that hypertension in the arms may be a manifestation of this defect. Boothby and Sandiford[23] found that the basal metabolic rate was over -10 per cent in 30 per cent of ninety-five cases of essential hypertension. The elevated basal metabolic rate in coarctation has been attributed by Grollman

and Ferrigan[20] to an increase in the circulation through the thyroid gland. In the observations now being reported, the oxygen consumption was normal, and the scatter of values was approximately the same as in a series of normal persons who were subjected to similar observations. Therefore, the increase in blood allotted to the periphery cannot be attributed to this factor. In fact, observations in pheochromocytoma[24] have shown that the peripheral blood flow is decreased, although the basal metabolic rate is increased. Moreover, although the body temperature was increased in the cases of coarctation, there was no rise in the basal metabolic rate.

Left axis deviation was the most common electrocardiographic abnormality; it occurred in seven cases. It probably arose from the increased work[3] placed upon the heart by the obstruction to the passage of blood through the aorta. Negativity of the T wave in Lead III, with or without coving, occurred in eight cases, i.e., with approximately the same frequency as left axis deviation. These T-wave changes were not those which are to be expected with left ventricular strain, which may be associated with alterations in the T waves in Lead I. Three subjects with a tendency to the lowest arm blood pressures had essentially normal electrocardiograms. As far as could be ascertained clinically, there were no other congenital defects in the one patient with right axis deviation to account for the divergence from the most common pattern.

Two patients of this series died, one of dissecting aneurysm of the arch of the aorta (Case 1), and the other (Case 3) of carcinomatosis, the primary location of which was in the larynx. Both of these patients showed negativity and coving of the T waves in Leads I and II, together with left axis deviation. Stewart and Bailey[3] found that alterations of the T waves with cardiac enlargement indicated a poor prognosis. It appears from the present analysis that the occurrence of changes in the T waves in Lead I, together with cardiac enlargement, is of grave prognostic importance, for the patients with changes in the T waves in Lead III alone, or with Lead II, are still living.

In all subjects except Case 1, who had only minimal constriction, the blood pressure in the arms was considerably higher than in the lower extremities (Fig. 3). The highest reading in the right arm was 200/110, and the lowest, 140/70, with comparable values in the left arm, although the latter measurement was slightly lower in the left arm in Cases 9 and 10. In Cases 3 and 5, the blood pressure could not be obtained in the lower extremities, and, in Cases 7 and 10, was obtained only in the left leg. In all cases, there was a small pulse pressure in the legs and a large one in the arms. The cause of the elevation of blood pressure in the arms and its decrease in the legs has been the subject of study. Mechanical obstruction to the flow of blood through the aorta has been suggested as the explanation.[1, 4, 25] Another point of view attributes it to a general increase in peripheral resistance.[26-28]

The effect upon blood pressure of constricting the aorta, experimentally,[7, 29, 30] has been observed. The opinion has been expressed that a pressor substance liberated by the kidneys, when their blood supply is reduced below a certain level, is responsible for this phenomenon, thereby
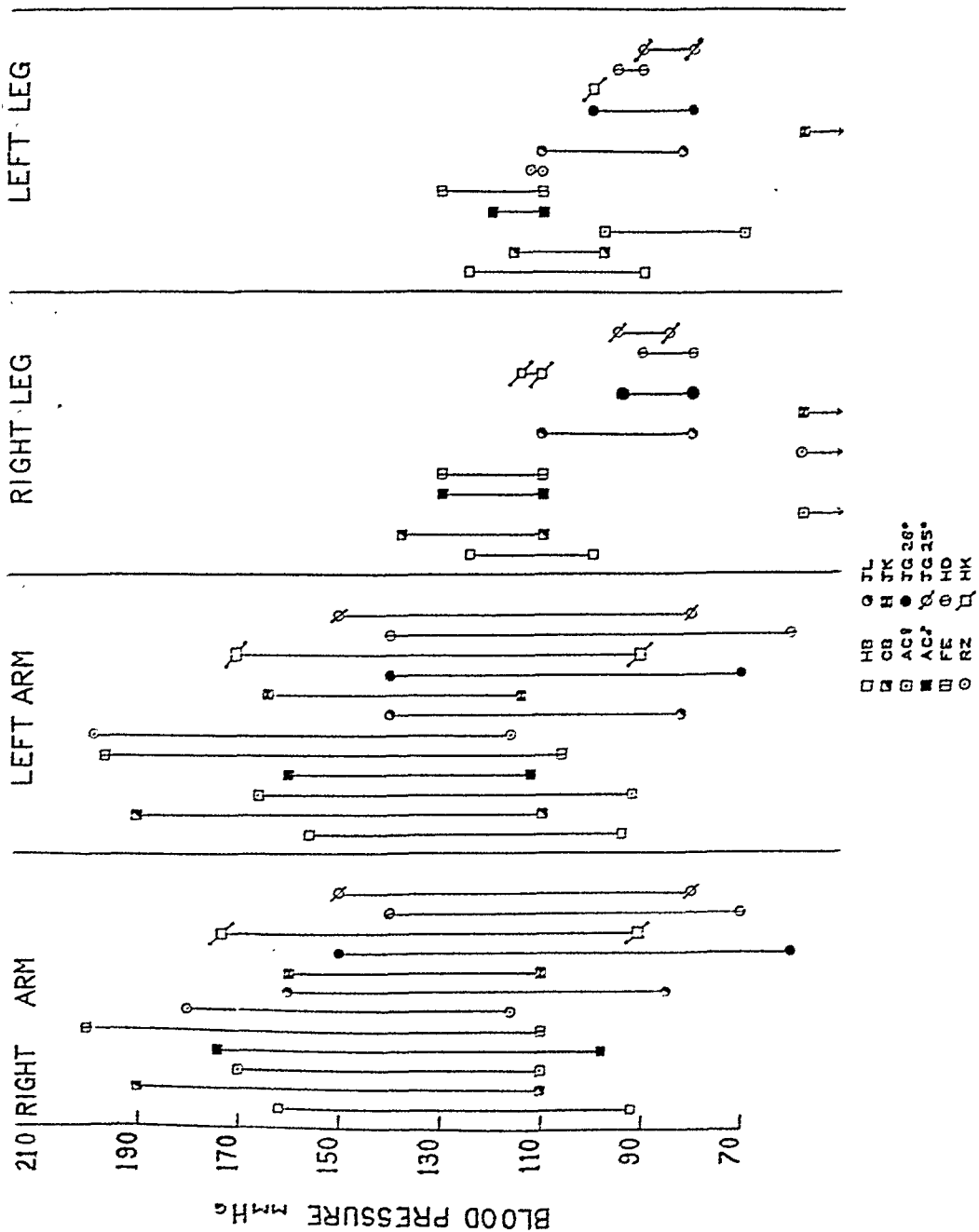
Fig. 3.—In this figure are recorded the blood pressures in the four extremities of twelve patients with coarctation of the aorta. Symbols with arrows pointing downward indicate that blood pressure readings were not obtainable.

bringing the cause of the hypertension in coarctation of the aorta into the framework of the Goldblatt kidney.[29] Castleman and Smithwick,[31] however, from a microscopic study of renal biopsies in 100 cases of essential hypertension in which splanchnicotomy was performed, came to the conclusion that evidence of renal vascular disease was insufficient to be the sole factor in the production of hypertension.

SUMMARY

1. Using a modification of the Hardy-Soderstrom method, the peripheral blood flow was measured in twelve cases of coarctation of the aorta; included in the data necessary for the calculations were measurements of basal metabolic rate and of rectal and skin temperatures. Measurements of skin temperature were made from 11 points on the body surface. In addition, circulation time was measured in ten subjects, electrocardiographic studies were made in eleven, and the size of the heart was estimated by means of teleoroentgenograms in ten.

2. The range of peripheral blood flow was from 14 to 129 c.c./sq. m./min., and the average was 68 c.c./sq. m./min. The range was greater and the average for the group was *higher* than in normal males, whose range was 8 to 84 c.c./sq. m./min., and the average, 33 c.c./sq. m./min. A larger volume of the cardiac output is allotted, therefore, to the periphery in these subjects than in normal persons. It is likely that an adequate blood supply was maintained in other parts of the body, for Stewart and Bailey[3] have shown that the cardiac output is increased in this condition.

3. The average of the weighted skin temperatures in the subjects studied was 33.63° C., that is to say, 0.81° C. higher than the value of 32.82° C. which was found in normal males. In general, the widest divergence from normal of temperatures for different areas was obtained in the upper half of the body. The increase in blood flow to the periphery accounts for the elevated skin temperature of these subjects.

4. The average rectal temperature was 37.33° C., compared to 36.72° C. for the normal group, that is to say, 0.61° C. higher.

5. Basal metabolic rates, when compared with the control group, fell within normal limits. The increased peripheral blood flow was not to be attributed to alterations in basal metabolic rate.

6. Circulation time was prolonged in some, normal in a few, and decreased in others. These observations are discussed.

7. The size of the heart, according to the cardiothoracic ratio, was greater than normal in only two of the patients who are still living.

8. The most common electrocardiographic abnormalities were left axis deviation and negativity and coving of the T waves in Lead III; these occurred in seven and eight cases, respectively. Two patients who showed coving in Leads I and II died. The others are still living. Three had essentially normal electrocardiograms; and one had right axis deviation.

9. Other clinical manifestations are summarized in Table III.

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DIFFERENTIATION OF THE ELECTROCARDIOGRAPHIC CHANGES PRODUCED IN THE DOG BY PROLONGED TEMPORARY OCCLUSION OF A CORONARY ARTERY FROM THOSE PRODUCED BY POSTOPERATIVE PERICARDITIS

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IN A study of postoperative pericarditis in dogs,[1] it was observed that RS-T junction displacements and primary T-wave changes regularly appeared seven hours after operation. The RS-T junction displacements reached a maximum about forty-eight hours after operation, and all electrocardiographic changes disappeared in five to nine days. Other studies[2, 3, 4] on brief, temporary, coronary occlusion in the dog show that the electrocardiographic changes produced by occlusions of thirty to ninety seconds appear at once with the onset of occlusion, and vanish within a minute or less after cessation of occlusion.

It cannot be emphasized too strongly that, in local ventricular pericarditis and in local ventricular ischemia and injury, the electrocardiographic changes are identical.[5, 6] Moreover, the magnitude of the associated RS-T junction displacements in any lead from the body surface cannot be safely used for etiological differentiation. The magnitude of the injury displacement is independent of the depth of injury and, among other things, is directly proportional to the area circumscribed by the surface boundary of the injured region.[7]

It is the purpose of this report to describe several experiments which were devised to test the interpretation offered by others[8-10] concerning the ''prolonged'' electrocardiographic changes associated with experimental, temporary occlusion of a coronary artery.

EXPERIMENT 1

DOG 1.—The anterolateral aspect of the pericardial sac was exposed in the usual way,[2] and the coronary artery was dissected and temporarily occluded for forty-two minutes. The electrocardiograms shown in Fig. 1 were obtained. The top curve in each row is a unipolar lead which was recorded with the exploring electrode on the pericardial sac, superjacent to the terminals of the dissected artery. The indifferent electrode was on the left foreleg. The bottom curve of each row is Lead I, which was recorded simultaneously by means of a two-string galvanometer of the Einthoven type.

Control 1 was recorded before opening the chest. Here, the exploring electrode was in the subcutaneous tissue superjacent to the apex impulse of the left ventricle. *Control 2* was recorded after opening the chest and before arterial dissection. The exploring electrode was on the pericardial sac, superjacent to the terminals of the yet undissected artery. The remainder of the strips are in the order recorded, and read from left to right, and from above down. The arrows over the top row indicate, respectively, the instant at which occlusion started, the instant at which the ligature was released, and the instant at which the artery appeared to be fully reopened. The dashed and double-dashed numbers over the strips indicate, respectively, the time in minutes and the time in seconds. In the unipolar lead the ischemia phase[4] is well developed eleven seconds after the commencement of occlusion. The injury phase[4] continues, although diminishing somewhat, throughout occlusion. The potassium (?) T effect of injury[4] is most pronounced in the eleven-minute strip. A small Q appears in the twenty-one minute strip and
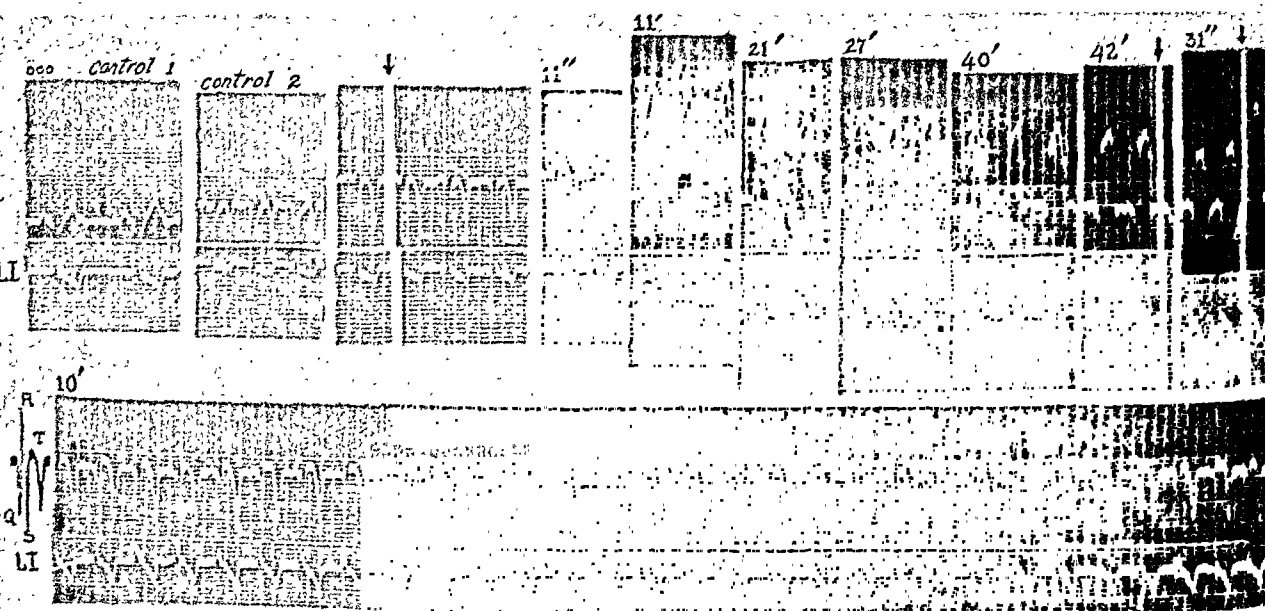
Fig. 1.—The effects produced by a forty-two minute occlusion. The top curve of each row is a unipolar lead recorded with the exploring electrode on the pericardial sac superjacent to the terminals of the dissected artery. Ten minutes after cessation of occlusion, the RS-T junction displacement in Lead I has vanished. The unipolar lead, recorded simultaneously shows a concurrent, subtotal reversion. The time lines are 0.1 second apart. Standardization is one-sixth normal and normal in the unipolar lead and in Lead I, respectively. See text.

continues to grow in amplitude in all subsequent strips. The temporary changes are like, in kind, in both leads, but are much more prominent in the unipolar lead. No QRS changes appear in Lead I which are comparable to the striking development of Q in the unipolar lead.

Partial reversion of the final ventricular deflections is present thirty-one seconds after cessation of occlusion. In the long strip, taken ten minutes after cessation of occlusion, reversion of the final ventricular

deflections of the unipolar lead is almost complete. The sketch on the left of the ten-minute strip is included for clarity. No definite reversion of the QRS change is present. In contrast to the unipolar lead changes, are the RS-T junction displacements in Lead I, which have vanished in less than ten minutes after cessation of occlusion. Here, complete reversion of the final ventricular deflections into the ischemia phase has taken place. The experiment was concluded, unwittingly, at this time because the movements of the galvanometer strings were judged to indicate complete reversion of the final ventricular deflections in both leads.
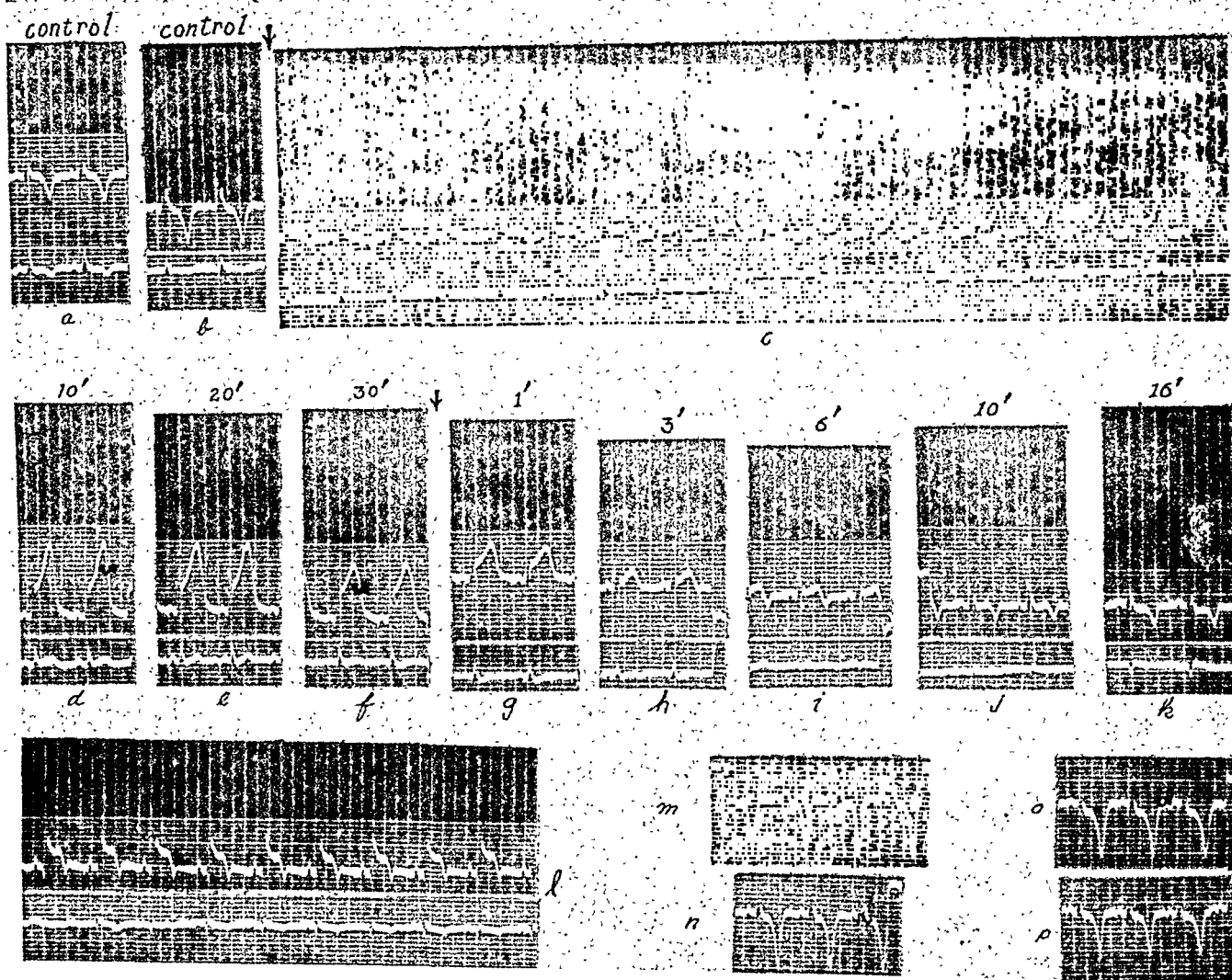
Fig. 2.—The effects produced by a thirty-minute occlusion and by local postoperative pericarditis. All changes due to the occlusion vanish within sixteen minutes after the occlusion ends (g through k). The effects of postoperative pericarditis are striking on the second postoperative day l. Concurrently, leads from the region previously involved by the occlusion show no abnormal changes (m through p). The time lines are 0.1 second apart. Standardization is one-sixth normal and normal in the unipolar lead and in Lead I, respectively. See text.

EXPERIMENT 2

Dog 2.—Using sterile technique, the anterolateral aspect of the pericardial sac was exposed and opened with a 2 cm. incision in the usual manner.[2] The anterior descending branch of the left coronary artery was dissected and occluded for thirty minutes. After a series of record-

ings the chest was closed. Forty-eight hours later the chest was reopened and additional recordings were made, after which the animal was sacrificed. The results are shown in Fig. 2. The order of recording reads from left to right and from above down. Each strip is composed of two leads recorded simultaneously. The top curve in strips a through k was taken with a unipolar lead in which the exploring electrode was on the pericardial sac superjacent to the terminals of the dissected artery (2.5 cm. from the incision in the pericardial sac in the direction of the apex of the left ventricle). The bottom curve is Lead I in strips a through l. Strips a and b were recorded before and after arterial dissection, respectively. Occlusion commenced in the interval between strips b and c. The latter strip shows the transition phase from ischemia into injury.[4] The dashed numbers over strips d, e, and f indicate the time in minutes after occlusion started. The dashed numbers over strips g through k indicate the time of recording after occlusion ended. After taking strip k the chest was closed. Clearly, the form of the unipolar lead reverts to that of the predissection control within sixteen minutes after the thirty-minute occlusion ends. The RS-T junction displacement almost vanishes within six minutes, i, and completely vanishes within ten minutes, j. No significant QRS changes appeared, either during or after the thirty-minute occlusion. The unreliable changes which developed concurrently in Lead I are noteworthy.

Strips l through p were recorded after the chest was reopened on the second postoperative day. When recording strip l, the exploring electrode rested upon the sutures in the pericardial sac superjacent to the site of arterial dissection. A striking RS-T junction displacement is present. Lead I likewise shows an RS-T junction displacement which, however, is small by comparison. Before recording strip m the exploring electrode had been moved 1 cm. away from the sutures in the direction of the apex of the left ventricle, and before recording strips n and o the electrode had been moved 2 and 3 cm., respectively, away from the sutured region toward the apex. At the latter site the pericardial sac was opened, and strip p was recorded from the heart's surface.

It is emphasized that strip l was recorded forty-eight hours after the effects produced by occlusion had vanished, and at the approximate time when the RS-T junction displacements due to local postoperative pericarditis are known[1] to be maximal. Moreover, the local character of the injury effect, confined as it is to that region of the heart's surface at the site of operation on the heart and pericardium, leaves little or no doubt concerning the interpretation that the effects are due to operative injury of the subepicardial muscle, rather than to any delayed, recurrent effect of occlusion. Finally, strips n through p were recorded with the exploring electrode superjacent to the terminals of

the previously occluded artery, as was the case for the top curve in strips *a* through *k*. The former strips are conspicuous, in that they display no RS-T junction displacements whatsoever.

Post-mortem examination revealed a zone of adherent pericarditis, 1.5 to 2 cm. in diameter, at the site of the three sutures which were used to close the pericardium. The remainder of the ventricular surface was smooth and free. However, the anterolateral aspect of the left ventricle displayed a delicate, milky, epicardial reaction.
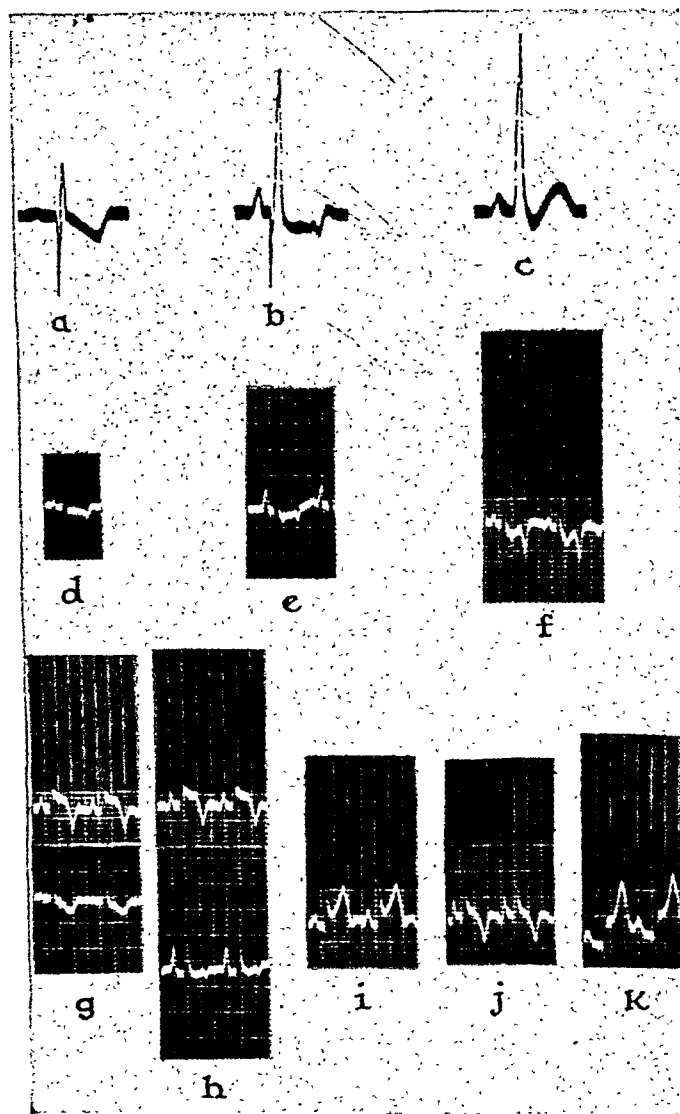
Fig. 3.—Curves from a control experiment showing the effects of local postoperative pericarditis (*g, h,* and *j*) as they appear on the second postoperative day. The time lines are 0.1 second apart. Standardization is normal in Leads I and II, and one-sixth normal in the unipolar lead. See text.

The general similarity of the final ventricular deflections of the unipolar leads in the early part of strip *c* and in strips *i* and *l* is notable. Is the electrocardiographic evolution of pericarditis similar to that of a region of myocardium which is temporarily robbed of its blood supply, similar to the extent that the injury effect in pericarditis is likewise preceded, as well as followed, by primary T-wave changes? Our clinical observations and experiments have not answered this question.

EXPERIMENT 3

DOG 3.—Using sterile precautions, a general procedure was carried out which was similar to that used with Dog 2. In the present instance, however, the pericardial sac was merely opened for thirty minutes and then closed with three sutures. The heart surface was not disturbed at the time of operation. Forty-eight hours later the chest was reopened and unipolar leads were recorded with the exploring electrode on, and in the neighborhood of, the sutured region of the pericardial sac. The results serve as a control, and are shown in Fig. 3. The enlarged sketches *a, b,* and *c* show, respectively, the appearance of Leads I and II and the semiunipolar lead taken with the exploring electrode in the subcutaneous tissue superjacent to the apex impulse of the left ventricle. Strips *a, b,* and *c* were recorded before, and strips *d, e,* and *f* were recorded after, opening the chest. For strip *f* the exploring electrode was on the pericardial sac at the site of subsequent incision (anterior to the tip of the left auricular appendage). The remainder of the strips in Fig. 3 were recorded after reopening the chest on the second postoperative day. The top curve in strips *g* and *h* was recorded with the exploring electrode on the sutured region of the pericardial sac. Here, the resemblance to strip *l* of Fig. 2 is striking. The bottom curves in strips *g* and *h* of Fig. 3 are Leads I and II, respectively, which were recorded simultaneously with the unipolar lead. Strips *i, j,* and *k* are unipolar leads taken with the exploring electrode in the neighborhood of the sutured region. When recording strip *i* the electrode was 2 cm. away from the sutured region in the direction of the ventricular apex. When recording strip *j* the electrode was 2 cm. inferior to the sutured region at the lateral margin of the left ventricle. A small RS-T junction displacement, ascribed to injury, is present. When recording strip *k* the electrode was on the heart's surface at the extreme apex of the left ventricle. The RS-T junction displacements shown in strips *i* and *k* are not ascribed to injury. They are due to effective early regression.[9]

Post-mortem examination revealed no pericardial adhesions. The epicardial surface showed a milky thickening confined to the region of the *g, h,* and *j* recordings. The epicarditis was most marked beneath the sutured region.

EXPERIMENT 4

DOG 4.—Using sterile precautions, a second control procedure was carried out in a manner identical to that used in Experiment 3, except that the incision in the pericardial sac was closed immediately. Forty-eight hours after operation the chest was reopened and the heart's surface was explored with the unipolar lead. The strips shown in the bottom row of Fig. 4 were obtained. Strips *a* and *b* are Leads I and II, respectively. Strip *c* was recorded with the exploring electrode on the zone of epicarditis produced by the superjacent operative procedure on
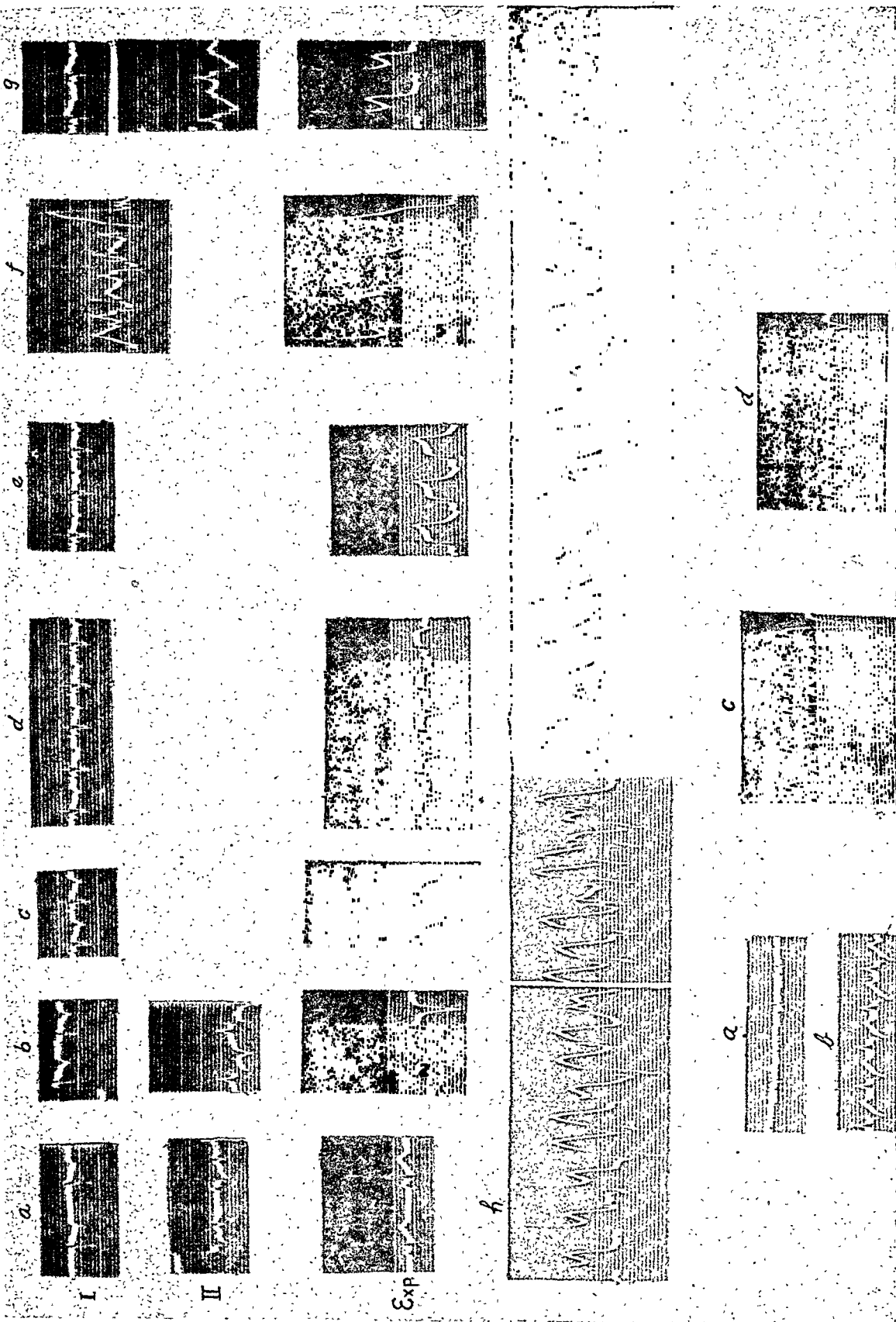
Fig. 4.—The bottom row contains four strips (*a*, *b*, *c*, and *d*) from a second control experiment in which the pericardial sac had been opened and promptly closed forty-eight hours prior to the time of the recordings. *a* is Lead I, *b* is Lead II, and *c* and *d* are unipolar leads from site of the epicarditis and from the neighboring, uninvolved ventricular surface, respectively. The top four rows contain strips from an experiment in which a forty-five minute occlusion (*b* through *h*) was carried out. Precisely at the end of the occlusion (see approximate time signal in strip *h*), ventricular fibrillation developed. Column *a* contains Leads I and II and the semiunipolar lead recorded with the exploring electrode in the subcutaneous tissue superjacent to the anterolateral wall of the left ventricle, before opening the chest. Column *b* shows similar leads after opening the chest and dissecting the segment of the anterior descending branch of the left coronary artery. Here, the exploring electrode is on the pericardial sac superjacent to the terminals of the dissected artery. The unipolar lead in columns *c*, *d*, and *e* shows the usual developmental stages (ischemia, transition from ischemia into injury, and injury, respectively) which immediately follow the onset of occlusion. Column *f* shows part of a volley of extrasystoles which occurred during the first ten minutes after the onset of occlusion. Column *g* contains strips recorded thirty-five minutes after the onset of occlusion. The time is five centimeters per second. Standardization is normal in the extremity leads and one-sixth normal in the unipolar leads. See text.

the pericardial sac. A rather striking RS-T junction displacement, due to injury, is present. Strip d was recorded with the exploring electrode on the heart's surface in the immediate neighborhood of the local epicarditis. No RS-T junction displacement is present. The abnormal form of the curve in strip c is due to a local postoperative pericarditis. Nevertheless, the curves in strips a and c present the same kind of changes which are observed in anterolateral infarction.

EXPERIMENT 5

Dog 5.—Using sterile precautions, a forty-five-minute complete occlusion of the anterior descending branch of the left coronary artery was produced in the usual way.[2] Upon release of the occlusion, ventricular fibrillation immediately developed and the animal died. The electrocardiograms which are shown in the *top* four rows of Fig. 4 were obtained before and during the occlusion. The form of the curves in strips f and h illustrates the two danger periods which are encountered in experiments on temporary occlusion. The first period occupies the initial ten minutes after the onset of occlusion, whereas the second period occurs with the release of the occluding ligature.

EXPERIMENT 6

Dog 6.—Using sterile precautions, the anterolateral aspect of the left ventricle was exposed in the usual way. A zone of epicardium 1 cm. in diameter was removed. The pericardial incision was then closed with three sutures. Electrocardiograms which were recorded before and during operation are shown within the inset in Fig. 5. The strips in column a' were recorded before operation. When taking a_0 the exploring electrode was in the subcutaneous tissue superjacent to the anterolateral aspect of the left ventricle. The strips in column b' were recorded after opening the chest. When recording strip b_0 the exploring electrode was on the anterolateral aspect of the pericardial sac. The strips in columns c' and d' were recorded immediately after closure of the pericardial sac. When strip c_0 was recorded the exploring electrode was superjacent to the region denuded of epicardium (which did not lie directly beneath the wound in the pericardial sac). A large RS-T junction displacement, ascribed to subepicardial trauma, is present. When recording strip d_0 the exploring electrode was on the pericardium superjacent to a region of normal ventricular wall near the apex. No RS-T junction displacement is present. At this stage of the experiment the chest was closed.

Fig. 5.—Within the insert are curves recorded before and during an operation in which a patch of epicardium was resected and the pericardial sac closed. The curves in columns a through i were recorded on the fourth postoperative day before, during, and after a fifty-minute occlusion. The effects produced by the occlusion (columns b through e) vanish within forty-five minutes (columns f through i) after cessation of occlusion. The strips in column a show the effects of postoperative pericarditis and, likewise, serve as a control for the occlusion effects. The time is five centimeters per second. The standardizations are shown. One millivolt was used for the extremity leads and three millivolts for the unipolar leads. See text.
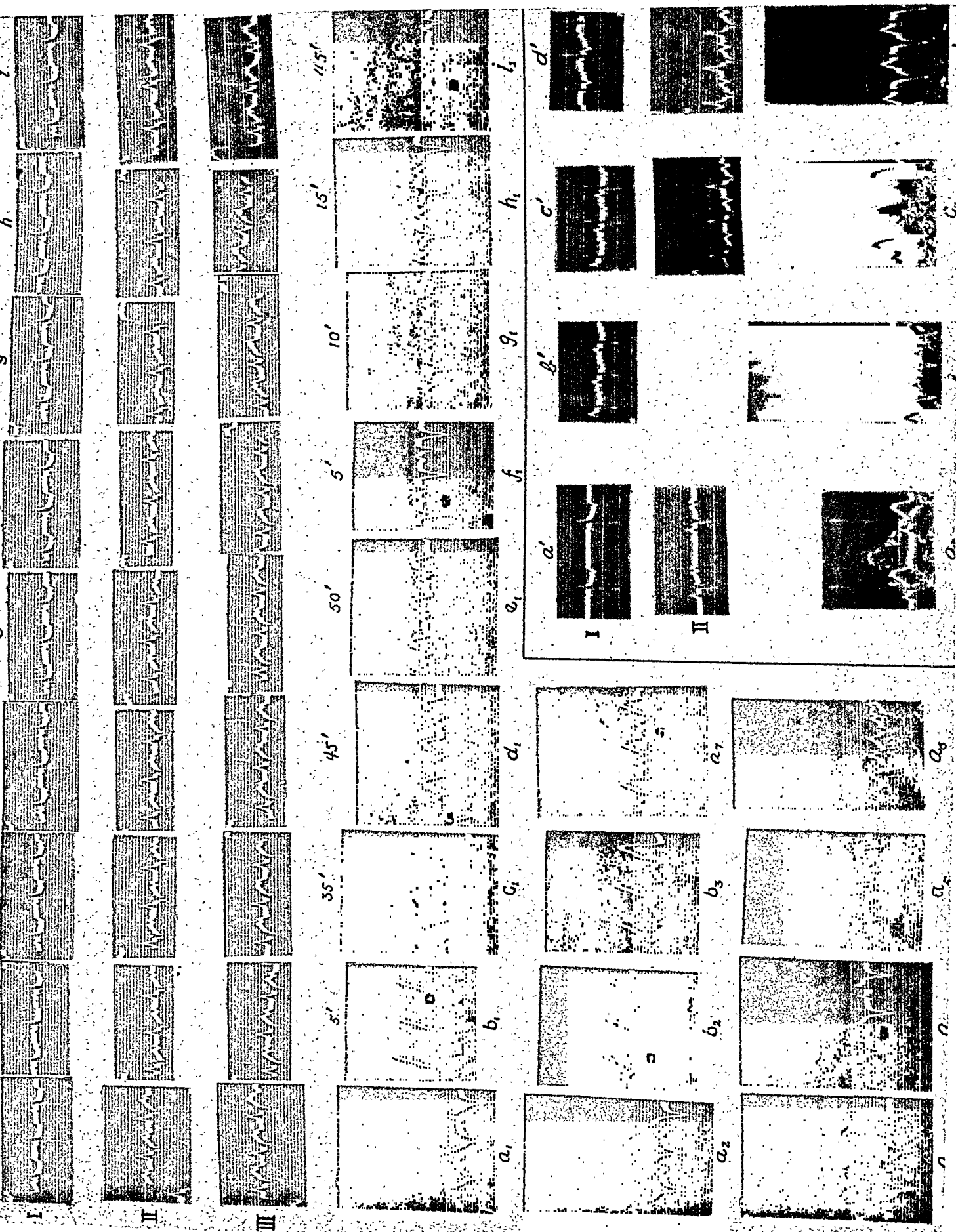
Fig. 5.—(*For legend see opposite page.*)

On the fourth postoperative day the chest was reopened and the anterolateral aspect of the pericardial sac was explored with unipolar leads. The two columns of strips under a and b of Fig. 5 were obtained. They include strips a_1 through a_7, for the recording of which the exploring electrode was placed on the pericardial sac at the following positions: for a_1, the center of the sutured region; for a_2, the anterior end of the sutured region; for a_3, the posterior end of the sutured region; and for a_4, a_5, a_6, and a_7, at 1, 2, 3, and 4 cm., respectively, from the sutured region on a line toward the apex of the left ventricle. RS-T junction displacement due to injury from postoperative pericarditis is present in all of the foregoing unipolar leads except a_5, a_6, and a_7. After taking the strips of column a the exploring electrode was returned to the a_4 position, where it remained throughout the rest of the experiment with one exception, i.e., strip b_2, which was taken with the electrode at the position of recording strip a_7. Upon return of the electrode to the position for recording a_4, the pericardial sac was reopened through the old incision. A ligature was passed around the anterior descending branch of the left coronary artery and the associated veins and was tied securely. Five minutes thereafter the strips in column b were recorded. After taking strip b_1 the electrode was moved for recording strip b_2, and was then promptly returned for recording strip b_3. At subsequent intervals (indicated by the dashed numbers over row four) the strips of columns c through i were recorded. Within the interval between columns e and f the fifty-minute occlusion was terminated. Only minor changes are observed in the standard Leads I, II, and III.

Throughout the first five minutes of occlusion the changes in the unipolar lead are striking. They are prominent, however, throughout the remainder of the occlusion period. The potassium(?) T effect is present in recordings b_1 and b_3, an effect which is slight in strips c_1 through e_1. The RS-T junction displacements ascribed to injury of occlusion remain nearly constant throughout the final fifteen minutes of occlusion and, concurrently, a prominent Q develops. Within the first ten minutes after termination of occlusion, the electrocardiographic changes produced by occlusion have practically vanished. Only a small RS-T junction displacement remains (strip g_1). In strips h_1 and i_1 no effects of injury are present.

The experiment shows that striking RS-T junction displacements due to local postoperative pericarditis may continue to exist through the fourth postoperative day. It likewise shows that changes in QRS and in the final ventricular deflections produced by a fifty-minute occlusion may disappear completely in fifteen minutes after the occlusion is terminated. As might be surmised from the appearance of the electrocardiographic changes, the artery occluded in Experiment 6 was not as large as that occluded in Experiment 1.

In 1937, Blumgart, et al.,[8] after experimenting with temporary coronary occlusion in cats, concluded that electrocardiograms "revealed anoxemic changes (due to occlusion) persisting during the postoperative days in all animals in which occlusion was maintained from five to forty minutes inclusive." In their controls only one animal was followed with serial electrocardiograms after the first postoperative day. In this connection it should be recalled that, in dogs, the RS-T junction displacements due to postoperative pericarditis do not reach maximum until the end of the second postoperative day. During a presentation of their work,[9] Dr. Blumgart asserted that, in excluding pericarditis as a cause for the prolonged electrocardiographic changes, they "relied entirely on decided S-T take-off changes and changes in the S-T segment." The changes they observed, however, became less pronounced *immediately* after cessation of occlusion (similar to our results in the dog). They also observed that the changes increased during the first few postoperative days (as did our changes in the dog which were due to postoperative pericarditis). They found no correlation between the duration of occlusion and the magnitude or duration of the observed electrocardiographic changes. Finally, they suggest that the pathologicophysiologic changes observed in their cat experiments are similar to those in man when angina pectoris is associated with persistent electrocardiographic changes and no coronary occlusion or myocardial infarction is found at autopsy.

Although we have not worked with cats, our observations on dogs do not permit us to accept the interpretations which they have placed upon their electrocardiographic changes. We believe that all the electrocardiographic changes (other than mechanism disturbances) which they obtained on and after the first postoperative day and which were ascribed by them to occlusion were actually due to postoperative pericarditis.

In 1941, Blumgart, et al.[10] working with dogs, found that temporary coronary occlusion which lasts from five to forty-five minutes "usually caused electrocardiographic changes which persisted for days to weeks." In curves from five control animals, they describe RS-T and T-wave changes which were like in kind to those obtained from animals undergoing temporary occlusion. They state that "only the changes which were different from, or much greater than, those observed in any of the control experiments were considered as definitely due to the effects of occlusion." It may be observed from their data that the average duration of occlusion which produced no significant electrocardiographic changes was twenty-four minutes, whereas the average duration of occlusion which produced significant electrocardiographic changes was twenty-seven minutes. Thus, they were able to find no correlation between the electrocardiographic changes, on the one hand, and the

duration of the occlusion (and the magnitude of the myocardial lesions), on the other. Their electrocardiographic interpretations were based upon extremity leads recorded before, during, and after occlusion.

Our results do not permit us to accept the interpretations which they have placed upon their electrocardiographic observations. We are convinced that all the electrocardiographic changes which they obtained on and after the first postoperative day and which involved the final ventricular deflections were due, as our experiments seem to prove, to a local postoperative pericarditis.

Our experiments show that RS-T junction displacements due to injury and produced by temporary occlusions of comparable duration vanish in less than thirty minutes after the occlusions are terminated. This is to be expected, for the muscle which "writes" the changes is not dead or irreversibly altered by deprivation of its arterial blood supply.[7] When coronary occlusion is permanent and the RS-T junction displacements persist for a week or two, it is not the infarcted muscle which "writes" the injury effect, but the perifocal zone of living muscle.[5] With temporary coronary occlusion, uncomplicated by arterial thrombosis, no such perifocal zone of muscle exists. The central region of the muscle ordinarily irrigated by the occluded artery remains in the injured state throughout occlusion and for a brief period thereafter.[4] Other things being equal, the duration of the latter period is directly proportional to the duration of occlusion.

At the present time we are not in position to deal fully with the nature of the QRS changes (Figs. 1 and 5) associated with temporary occlusion. It is our present opinion, however, that the breakdown of the QRS complex in unipolar leads recorded with the exploring electrode superjacent to the involved muscle is rather closely connected with irreversible deterioration of the subjacent myocardium. Electrocardiographic changes of this kind, which continue for days after temporary occlusion, should show a close correlation with gross and/or microscopic evidence of local muscle death. Other factors being equal, the difference in serial electrocardiographic changes due, on the one hand, to permanent coronary occlusion and myocardial infarction, and, on the other hand, to temporary occlusion and myocardial infarction, is, we contend, entirely confined to the duration of the changes in the final ventricular deflections—a duration which is prolonged in the case of the former, and brief in the case of the latter. Moreover, since the same kind of changes occur in the final ventricular deflections in the presence as well as in the absence of myocardial infarction,[2-4] emphasis is justly placed on the occurrence of certain permanent QRS changes for reliable aid in the electrocardiographic diagnosis of myocardial infarction.[5]

Unlike Blumgart, et al.,[10] we find no evidence that there is a relationship between the persistent electrocardiographic changes which

may follow certain attacks of angina pectoris in man, and the persistent changes which are associated with experimental temporary coronary occlusion. The former may be ascribed to persistent, acute, local ventricular ischemia which, in turn, is due to a concurrent, local, subtotal occlusion. The latter are certainly due to a local postoperative pericarditis. Our explanation of the electrocardiographic changes which may follow an attack of angina pectoris does not specify the mechanism of occlusion. Conceivably, the mechanism might differ in different instances. The explanation likewise involves the problem of cardiac pain. The site of origin of cardiac pain is still unsettled. We believe the available evidence favors the idea that cardiac pain results from impulses which originate in the walls of the coronary system. Thus, the occurrence of painless myocardial infarction, the occurrence of severe attacks of cardiac pain without infarction and with or without associated electrocardiographic changes, and the occurrence of painless, acute, and chronic local ventricular ischemia are explainable.

SUMMARY

1. A method is presented by which the electrocardiographic changes due to experimental coronary occlusion may be differentiated from those caused by the associated postoperative pericarditis.

2. It is shown that the changes in the final ventricular deflections which are due to experimental, temporary, coronary occlusions of fifty minutes, or less, vanish completely within thirty minutes after cessation of occlusion, and that the changes which appear on and after the first postoperative day are caused by local postoperative pericarditis.

3. Other factors being equal, the duration of the electrocardiographic changes which immediately follow cessation of occlusions of fifty minutes, or less, is directly proportional to the duration of the occlusion.

4. There are no differences in the magnitude or in the kind of electrocardiographic changes which are produced by acute local ventricular ischemia and injury, on the one hand, and by local postoperative pericarditis, on the other. The former occur during, and for a brief time after, temporary occlusion. For the most part, the latter occur on and after the first postoperative day. The site of generation of the electrical effects which account for the two etiologically different groups of changes is different, i.e., the electrical effects associated with occlusion are generated in the muscle ordinarily irrigated by the occluded artery, whereas those associated with postoperative pericarditis are generated by the muscle adjacent to the local epicarditis which results primarily from the trauma of dissection of the coronary artery and from the trauma caused by the sutures which are used to close the pericardial sac.

5. These observations differ decidedly from those of others.[8-10] We ascribe the differences to the use, by others, of extremity leads only.

It is important not to rely entirely upon extremity leads for an evaluation of the electrocardiographic changes which occur in association with animal experimentation.

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EFFECT OF DEHYDRATION, PRODUCED BY MERCUPURIN, ON THE PLASMA VOLUME OF NORMAL PERSONS

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I T HAS been assumed[1,2] that the plasma volume remains relatively constant with dehydration because it is protected by the much larger extracellular fluid volume. Using improved techniques for measurement of the plasma volume, however, it has been found that considerable decreases in the plasma volume may be associated with dehydration induced in animals by removal of intestinal fluid[3] or the intraperitoneal injection of glucose,[4] and in man by diabetic acidosis[5] and the administration of ammonium chloride.[6]

There is considerable variation of opinion concerning the mode of action and the effectiveness of mercurial diuretics in different diseases because of the variability in the diuretic response from patient to patient as well as in a single patient. When edema is present, it is difficult to evaluate the role played by diuretic drugs because of the spontaneous variations in the pathologic process. In general, it may be said that the diuretic response in patients with heart failure is roughly proportional to the amount of edema.[7]

There is little information[8] concerning the action of mercurial diuretics on normal subjects, and, consequently, there is no standard upon which diuresis may be evaluated. Occasionally, these diuretics are administered to patients who no longer exhibit clinical evidence of edema, and, when diuresis results, it may be interpreted as evidence of "subclinical edema."

These observations were made on normal subjets in an effort to establish a base line by which the diuretic effect of a single dose of one organic mercurial compound might be evaluated, and to assay the effect of this type of dehydration upon the plasma volume.

METHODS

Ten patients in good health, who were free from cardiovascular or renal disease and had never had edema, were selected as normal subjects for study. Each subject had been on the routine hospital diet, with fluid and salt ad lib., for several days before the observations, and was presumably in a "normal state of hydration."

On the day the observations were started, the subject was weighed in the rested, postabsorptive state on a beam balance which was accurate to

2 grams. After the weighing, he was placed on a table, and blood samples were taken for determination of the plasma volume,[9] hematocrit,[10] and serum proteins.[11] After forty-five minutes on the table, estimations of the arterial and venous blood pressures[12] were made. and, at the conclusion of the observations, 2 c.c. of mercupurin were injected, intravenously. During the day, the patient was allowed fluids ad lib. and consumed all the food on his trays. The following morning the subject was again weighed, and the observations were repeated while he was in the rested, postabsorptive state.

If the subject consumes his usual diet. changes in weight from one day to the next will reflect closely changes in the water content of the body. It can, therefore, be assumed that the weight lost twenty-four hours after an injection of mercupurin closely approximates the diuresis produced. The error of such an assumption is of little significance in dealing with the large changes in weight which were observed.

Control determinations of the plasma volume and hematocrit were repeated twenty-four times on successive mornings on twenty-two normal subjects. There was a mean difference between the determinations of plasma volume of $+27.5 \pm 19.1$ c.c., or $+0.95 \pm 0.64$ per cent of the initial volume, and a mean percentage change in the hematocrit of -0.75 ± 0.52. In thirteen repeated determinations of the total serum protein. there was a mean percentage change of -0.60 ± 1 per cent.

RESULTS

All subjects experienced a diuresis, and in every case there was a fall in the plasma volume, associated with an increase in the hematocrit reading and serum protein concentration. The changes in plasma volume, serum protein concentration, hematocrit, venous pressure, and body weight are presented in Table I. The percentage change expresses the variations in plasma volume for the group more accurately than the actual change, for the plasma volume will vary considerably with the size of the subject.

Although all of the subjects had a diuresis, there was considerable variation in the degree of response. The average weight loss was 1.73 ± 0.3 kg., or 2.64 ± 0.5 per cent of the body weight. Two subjects. No. 2 and No. 10, had a 3.5 kg. weight loss, while two others lost only 0.5 and 0.7 kg., respectively. The larger subjects underwent a greater change in weight than the smaller ones.

The fall in plasma volume was roughly proportional to the extent of diuresis. The average decrease in the plasma volume was 544 ± 87.7 c.c., or -15.7 ± 2.4 per cent of the initial plasma volume. In two cases, No. 7 and No. 9, the change in the plasma volume was small, and in each instance the diuresis was considerably below the average for the group. The percentage increase in serum protein concentration and hematocrit was considerably less than the decrease in plasma volume. The average change in serum proteins was -0.74 ± 0.14 Gm., or $+11.5 \pm 2.6$ per cent. There was a mean increase in the packed cells of the hematocrit of 2.9 ± 0.6. which represented a mean percentage change of only $+6.9 \pm 1.8$.

TABLE I

CHANGES TWENTY-FOUR HOURS AFTER THE ADMINISTRATION OF 2 C.C. OF MERCUPURIN TO TEN NORMAL SUBJECTS

CASE	CHANGE IN PLASMA VOLUME (C.C.)	CHANGE IN PLASMA VOLUME (%)	CHANGE IN TOTAL PROTEIN CONCENTRATION (GM.)	CHANGE IN TOTAL PROTEIN CONCENTRATION (%)	CHANGE IN HEMATOCRIT	CHANGE IN HEMATOCRIT (%)	CHANGE IN BODY WEIGHT (KG.)	CHANGE IN BODY WEIGHT (%)	SYSTOLIC BLOOD PRESSURE BEFORE MERCUPURIN	SYSTOLIC BLOOD PRESSURE AFTER MERCUPURIN	DIASTOLIC BLOOD PRESSURE BEFORE MERCUPURIN	DIASTOLIC BLOOD PRESSURE AFTER MERCUPURIN	CHANGE IN VENOUS PRESSURE (MM. SALINE)
1	-580	-20.2	+1.56	+26.5	+3.8	+ 6.5	-1.2	-1.8	120	108	84	86	-25
2	-820	-21.5	+1.08	+17.5	+1.4	+ 2.9	-3.5	-4.5	130	112	84	88	-11
3	-350	- 9.9	+0.77	+11.2	+3.0	+ 7.3	-1.5	-2.5	116	90	70	72	-17
4	-490	-14.0	+0.59	+ 9.0	+1.9	+ 4.5	-0.5	-1.0	120	110	82	84	-38
5	-880	-28.1	+0.72	+10.1	+2.1	+ 4.4	-2.0	-2.7	114	110	80	92	-25
6	-790	-19.5	+0.31	+ 4.6	+1.0	+ 2.4	-0.9	-1.4	105	100	74	82	-18
7	-180	- 6.1	+0.60	+ 9.8	+2.7	+ 5.8	-0.7	-0.9	120	120	84	86	- 5
8	-520	-13.1	+0.30	+ 3.5	+6.5	+18.0	-2.7	-4.3	100	100	76	86	-45
9	- 70	- 3.5	--	--	+0.3	+ 0.8	-0.9	-1.7	90	92	70	70	- 5
10	-760	-21.2	--	--	+6.0	+16.7	-3.5	-5.6	110	105	70	90	-63
Mean	-544	-15.7	+0.74	+11.5	+2.9	+ 6.9	-1.73	-2.64	112.6	104.8	77.4	83.6	-25.2
S.D.	263	7.3	0.37	6.9	1.9	5.5	1.0	1.5	9.7	7.7	6.3	6.4	16
S.E.	±87.7	± 2.4	±0.14	± 2.6	±0.6	± 1.8	±0.3	±0.5	± 3.2	± 2.6	±2.1	±2.1	±5.3

Accompanying the diuresis there was a fall in the venous pressure in every case; in some instances this was quite striking, whereas in others it was of little significance. There was an average decrease of 25.2 ± 5.3 mm. of saline from the control determination. The control venous pressure measurements were all normal, ranging from 70 to 136 mm. of water. There was no significant relationship between the control level of venous pressure and the degree of change. The changes that were most pronounced occurred in Cases 4, 8, and 10, in which the control venous pressures were 78, 120, and 100 mm. saline, respectively. In general, the fall in venous pressure roughly paralleled the decrease in plasma volume and body weight. There was also a significant decrease in the pulse pressure, with a rise in the diastolic pressure and a fall in systolic pressure.

The majority of the subjects observed no change in their state of well-being except some increase in lassitude. A few noted a sensation of weakness and tiredness in the supine position, with dizziness and light-headedness on standing. This was particularly evident in Cases 1, 5, and 10.

DISCUSSION

There are many conflicting reports in the literature concerning the changes in the plasma volume after giving mercurial diuretics. This conflict is probably the result of deductions drawn from slight variations in the constituents of the plasma, from differences in the time the observations were made, and, possibly, from different types of experimental material.

Many investigators have used alterations in the concentration of serum proteins as an index of change in plasma volume. Some[13] reported decreases in the plasma protein concentration shortly after the injection of a mercurial diuretic, followed later, in some instances, by a rise in the plasma protein. Others[14] observed no decrease in the plasma protein, but a consistent increase in its concentration during and after the period of diuresis. Studies based on techniques that measure the plasma volume directly also are in disagreement. Feher[15] found that there was an elevation of the plasma volume either at the height of the diuresis or after diuresis. Brown and Rowntree[16A] and Swigert and Fitz[16B] found changes in the blood volume in either direction. Goldhammer, et al.,[17A] Evans and Gibson,[17B] Calvin and Decherd,[17C] and Herrmann and Decherd[17D] reported that consistent decreases in the plasma volume were present with the onset of diuresis and at the completion of diuresis.

The changes in protein concentration and plasma volume have been used to support theories concerning the action of mercurial diuretics. The demonstration of a decrease in plasma protein concentration and an increase in plasma volume is used to support the theory that these drugs act on the tissues and mobilize tissue fluid. The observers who found increases in protein concentration and decreases in plasma volume consider that these changes are evidence of direct action of the mercurial diuretics on the kidney. This view receives strong support from the work of Goverts,[18] Christian and Bartram,[19] Herrmann, et al.,[20] and Blumgart et al.,[7, 8] who have approached the problem in a different manner. If the action of mercurials is directly on the kidneys, presumably through diminished tubular absorption as the preponderance of more recent work would suggest, then the plasma volume should fall as tubular absorption is impaired, unless it is completely protected by the extracellular fluid. There would appear to be no reason to expect an increase in plasma volume under these circumstances unless protein were added to the blood stream, as suggested by Nonnenbruch. There is no evidence, however, that protein is added to the blood stream; it may actually be lost in certain instances.[21, 22]

The results reported here cannot answer the question whether there are shifts in the plasma volume before or at the time of diuresis. The measurement of plasma volume twenty-four hours after the injection of mercupurin will reflect only the end result of the diuresis. As such, however, there appears to be no suggestion that hydremia has occurred. It is also evident that the plasma volume is not well supported by the extracellular fluid volume.

If the action of mercurial diuretics is directly on the kidney, it might be expected that the plasma volume of normal subjects would suffer greater changes in proportion to the fluid lost than that of an edematous subject, which is presumably supported by a larger volume of extra-

cellular fluid. This may, in part, explain the inconsistent results of Swigert and Fitz [16B] and others who studied edematous patients. It does not explain an increase in the plasma volume after diuresis, and this did not occur in the cases reported here.

Blumgart, et al.,[8] in a careful balance study of two normal subjects who were undergoing salyrgan diuresis, calculated that 90 per cent of the water lost under these circumstances comes from the extracellular fluid, and only 10 per cent from the tissues. The results in these ten subjects indicate that the decrease in plasma volume contributes greatly to the weight lost. The loss of plasma volume would account for 39.6 ± 9.5 per cent of the decrease in body weight. In Cases 4 and 6, the decrease in plasma volume accounted for nearly all of the change in body weight. If these cases are eliminated, the change in plasma volume in the remaining eight cases accounts for 26.3 ± 3.8 per cent of the weight lost. This is in striking contrast to the effect of ammonium chloride diuresis in a similar group of normal subjects,[6] in which the decrease in plasma volume accounted for only 12.2 ± 1.2 per cent of the weight lost.

It is interesting that the average diureses observed in this group of normal subjects after 2 c.c. of mercupurin, namely, 2.6 per cent of the body weight, was less than that which occurred in a similar group on a low-salt diet and ammonium chloride;[6] the latter had an average diuresis of 4.4 per cent of the body weight after a three- or four-day period. Ordinarily, patients with edema do not have a greater diuresis with ammonium chloride than with mercupurin. This discrepancy in these normal subjects may be explained by the fact that, with ammonium chloride, water is lost from both fluid compartments in nearly equal amounts,[23] whereas, with mercupurin, water is lost largely from the extracellular fluid compartment. Thus, in the absence of abnormal accumulations of extracellular fluid, ammonium chloride administration might be expected to produce a greater weight loss.

These results suggest that a normal subject may have a diuresis of 2 to 6 pounds, or 1 to 4 per cent of the body weight, in response to a 2 c.c. injection of mercupurin. At times, after a patient has recovered from congestive heart failure, diuretics are still used when there is no longer clinical evidence of edema. When a diuresis of six pounds or less occurs in such cases, it should not necessarily be interpreted as evidence of abnormal accumulations of edema fluid, and should suggest that further diuresis may not be necessary. Such a diuresis should not be interpreted as evidence of "subclinical edema." Furthermore, the administration of mercurial diuretics to such patients may produce severe dehydration and the clinical picture characterized by weakness, apathy, delirium, and, at times, unconsciousness, described by Poll and Stern.[24]

The failure of the concentration of serum protein and the hematocrit readings to increase in proportion to the fall in plasma volume under these circumstances has been noted before.[25] This again is evidence that shifts in these components fail to reflect quantitatively the change in plasma volume, although they may indicate that the plasma volume is undergoing changes, and the direction of the change.

The consistent fall in the venous pressure in these cases appears to be related to the decrease in plasma volume and body weight. Large changes in the plasma volume, with two exceptions, Cases 2 and 6, were accompanied by pronounced changes in the venous pressure. Since the veins of the forearm are a series of collapsible tubes, the pressure in them is dependent upon the pressure of the surrounding tissues,[25] the intrathoracic pressure,[28] and the pressure in the right auricle.[27] Ryder, Molle, and Ferris[26] have indicated that the pressure in a peripheral vein in normal subjects is a function of tissue pressure causing collapse of that vein along its course to the heart, so that it is independent of the auricular pressure. Richards, et al.,[27] found a gradient of 39 mm. of water between the antecubital venous pressure and the auricular pressure in nine normal subjects. The gradient tends to disappear as the pressure in the auricle rises in congestive heart failure. The pressure in the peripheral veins is not changed by decreases in the intrathoracic pressure below normal, but will be affected by increased intrathoracic pressure.[28] Another factor, however, must be considered in evaluating the decrease in venous pressure. Warren and Stead[29] found that, with pooling of blood in the lower extremities of six normal subjects, there was a fall in the antecubital venous pressure of 23 mm., and, in the external jugular pressure, of 53 mm. Under these circumstances, the decrease in the amount of blood returning to the auricle was the chief factor affecting the venous pressure, and it would appear that either the volume of blood flow or the auricular pressure, or both, had some effect on the peripheral venous pressure.

The fall in venous pressure after the injection of mercupurin may be explained by several factors. The loss of extracellular fluid in the tissues surrounding the antecubital vein may result in a decrease in tissue pressure. In these cases, the weight loss was relatively small, and it appears unlikely that this factor would be of great importance. The decrease in arterial pulse pressure and the symptoms of weakness and apathy at rest in bed and dizziness and faintness in the upright position experienced by some of these subjects suggest that there was a decrease in the blood flow. This might produce the fall in venous pressure as a result of the decreased filling of the vascular bed in the region of the antecubital vein, thereby decreasing the tissue tone. The decrease in blood flow, if present, may be the result of a decrease in the auricular pressure associated with the lower plasma volume, which may be reflected by the fall in the antecubital venous pressure. The failure to demonstrate more consistent changes in the venous

pressure under these circumstances may be the result of individual variation in the degree of local obstruction to the flow of blood in the antecubital vein, which thus masks changes in the auricular pressure.

The symptoms exhibited by some of these normal subjects are similar in many respects to those noted by edematous subjects after extensive diuresis,[24] and suggest that diminishing blood volume may play an important role. The clinical picture of apathy, weakness, delirium, and unconsciousness after extensive diuresis and the symptoms associated with a diminished blood volume which were noted by the normal subjects are analogous, in many ways, to the clinical appearance and circulatory defect of shock.

SUMMARY

1. Plasma volume, serum protein concentration, hematocrit value, arterial and venous blood pressures, and body weight were determined in ten normal subjects before, and twenty-four hours after, the injection of 2 c.c. of mercupurin.

2. There was a fall in plasma volume in every case, averaging 544 ± 87.7 c.c., or 15.7 ± 2.4 per cent of the control determination; an average rise in serum proteins of 0.74 ± 0.14 Gm., or 11.5 ± 2.6 per cent; and an average rise in hematocrit of 2.9 ± 0.6, or 6.9 ± 1.8 per cent.

3. A diuresis was experienced in every case; the mean was 1.73 ± 0.3 kg., or 2.6 ± 0.5 per cent of the body weight.

4. Associated with the diuresis and decrease in plasma volume, there was a fall in venous pressure and pulse pressure.

5. In some instances, the subjects exhibited weakness, apathy, dizziness, and faintness, suggesting a diminution in cardiac output.

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Clinical Report

SUCCESSFUL USE OF A MASSIVE DOSE OF QUINIDINE IN A CASE OF INTRACTABLE VENTRICULAR TACHYCARDIA

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VENTRICULAR tachycardia is very serious in conjunction with advanced heart disease. It has been produced experimentally by ligation of the coronary arteries.[1] Apparently, in such cases, the ischemic area becomes irritable, and hence becomes the source of this idioventricular rhythm.

A case of ventricular tachycardia is described in which a very large dose of quinidine (185 grains) over a relatively short period of time (two and one-half days) was required to establish normal rhythm. It was thought worth reporting to show the relative safety of a huge amount of quinidine in cases of intractable ventricular tachycardia, providing serial electrocardiographic studies are made before each dose in order to study the QRS complex.

CASE REPORT

J. F., an attorney, aged 56 years, complained of a sudden, pressing, substernal pain which spread to the entire upper part of the chest and down both arms, and finally localized in the substernal region. This was accompanied by vomiting. Although the past history was entirely negative, the family history was of interest. The patient's mother died of a heart attack at the age of 53 years, his father died of a cerebral hemorrhage at the age of 65 years, and his sister had had coronary thrombosis two years previously. His habits were very regular, and he had played golf weekly until his present illness.

Examination.—Examination revealed normal temperature and respirations, with a regular pulse at a rate of 80 per minute. The patient was cold, slightly ashen, and nauseated. The eye grounds showed slight arteriosclerosis, without hemorrhages or exudates. The lungs were entirely normal. The cardiac apex was in the sixth intercostal space, 3 cm. outside the midclavicular line. The sounds were of very poor quality. There were no thrills, murmurs, or friction rubs. The blood pressure was 116/88.

Course.—A single dose of morphine, with atropine sulfate, and small doses of quinidine were employed the first day. The following day, the pain was relieved and normal color had returned. The patient's lungs were normal and the quality of the heart sounds improved. About thirty-six hours after the attack, he suddenly coughed up rusty sputum, and examination revealed slight dullness and fine, crepitant rales at the base of the right lung. Examination of the sputum revealed a

Type XII pneumococcus. The leucocyte count was 13,500, with 78 per cent polynuclears. The icteric index was 4.5. The next morning the temperature rose to 102° F., and there was consolidation of the right lower lobe, which spread to the base of the left lower lobe. There was a favorable response to sulfadiazine. On the sixth day, a precordial friction rub synchronous with the heart beat was heard; it was loudest at the xiphoid and lasted six days. On the fourteenth day there was another slight rise in temperature; this fever subsided rapidly when sulfadiazine was given. Although tubular breath sounds were no longer present, medium moist râles remained at the bases of both lower lobes, and were attributed to persistent pneumonitis. On the sixteenth
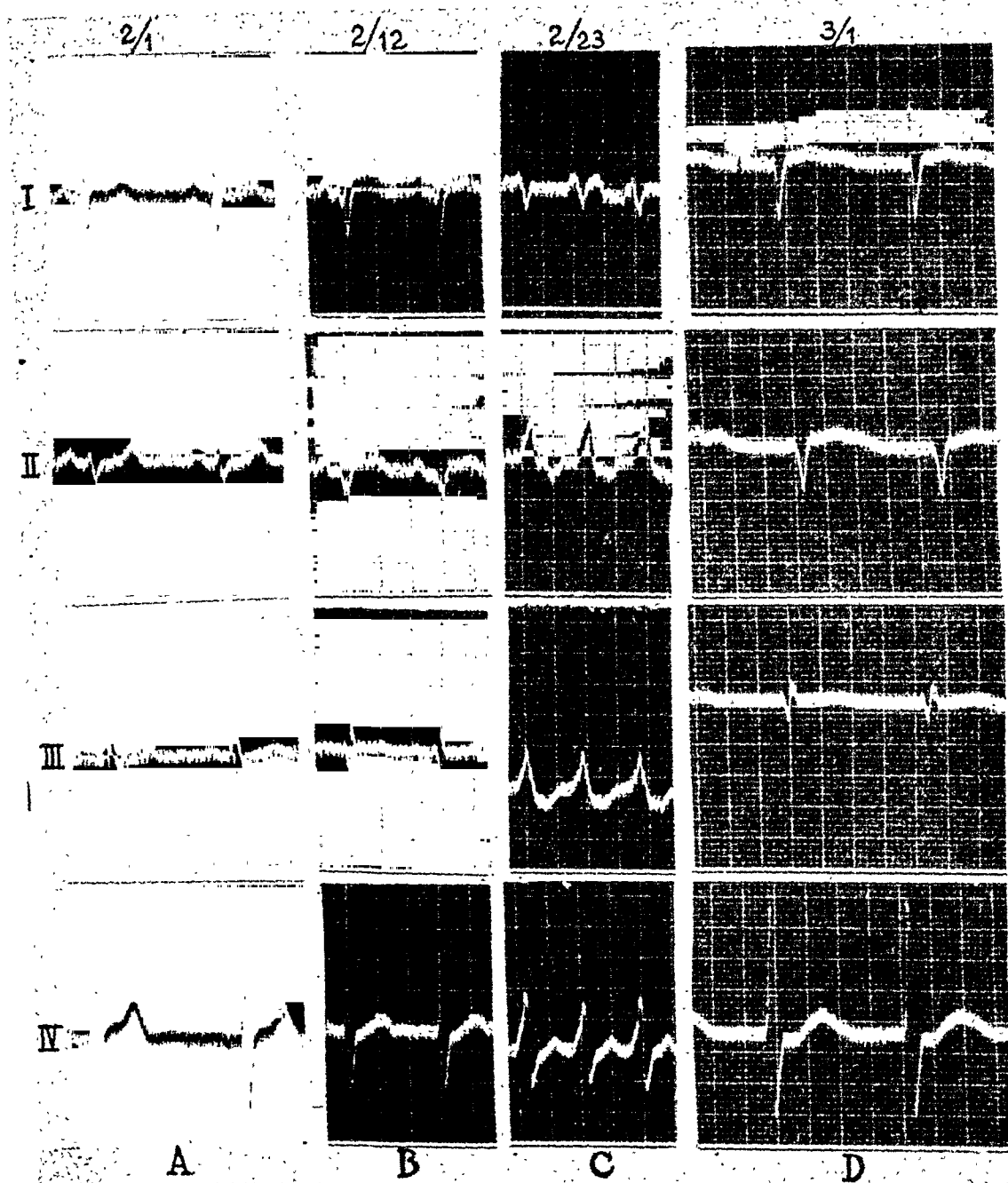
Fig. 1.—A, Ten hours after onset; no significant changes. B, Twelve days later; Lead I: small R wave with increased prominence of S wave; Lead II: notched S wave; elevation of RS-T segment in first three leads; suggestion of acute right ventricular strain. C, Ventricular tachycardia. D, After 185 grains of quinidine, heart rate fell to 68; P-R interval, 0.58 second, returned to normal spontaneously four hours later.

day there was a second attack of precordial pain, and the blood pressure fell to 90/70. The following day the heart rate rose suddenly to 180 beats per minute. This was uninfluenced by carotid sinus or eyeball pressure (Fig. 1). It was decided to give 10 grains of quinidine approximately every two hours. An electrocardiogram was taken before every dose for study of the rate, rhythm, and the QRS interval. It was imperative not to allow this interval to exceed 0.18 second because of the danger of ventricular fibrillation and death. A total of 185 grains was given in two and one-half days, with a free interval of ten hours (Table I).

TABLE I

DAY	HOUR	BLOOD PRESSURE	PULSE	QUINIDINE DOSAGE IN GRAINS
Friday	4:30 P.M.	84/76	180	10
	6:30	84/70	154	10
	8:30	80/62	138	10
	10:23	Not obtainable	126 Very irregular and thready	½ ampoule cora-mine 3 minims adrenalin
	11:30	82/72	134	-
Saturday	2 A.M.	88/72	134	10
	4	80/74	144	10
	6	80/70	130	10
	8	78/66	112	5 (Vomiting)
	10	78/62	110	5 (Vomiting)
	Discontinued for ten hours because of vomiting			
	8 P.M.	86/70	120	10
	10:30	86/70	112	5
	11:45	88/70	120	5
Sunday	2 A.M.	96/68	116	10
	7	86/62	118	-
	11:45	98/78	120	10
	4:15 P.M.	90/66	130	10
	6:30	86/68	120	10
	8:30	90/70	110	10
	10:15	86/68	110	10
Monday	12:30 A.M.	84/60	114	10
	2:30	84/60	106	10
	4:30	84/60	104	10
	6:30	84/60	68	5
	3:00 P.M.	92/70	62	-
	5:00	92/68	58	-
	10:00	115/86*	72*	-

*The pulse and blood pressure have remained at this level for the past fifteen months.

COMMENT

This case illustrates decisively the specific effect of quinidine on ventricular tachycardia when it is given in sufficient dosage. We, as well as others,[2,3] believe that this is the largest dose of quinidine sulfate ever given over such a short period of time.

Continued ventricular tachycardia presents a serious situation. It is obvious that the heart of a man 56 years of age cannot maintain, for long, a rate of 150 to 200 beats per minute. Therefore, the gravity of the event warrants the risks involved in giving quinidine in very large

doses. The exact dosage is variable, and should be ascertained, not by trial and error, but by electrocardiographic studies before each succeeding dose is given. This is important because the degree of myocardial poisoning must be carefully evaluated before the next dose can be given in order to prevent serious cumulative effects. The duration of the QRS complex was employed as an index of such poisoning. An increase up to 25 per cent is allowable.[4] Any further prolongation increases the danger of fatal ventricular fibrillation. Other causes of death which must be kept in mind are respiratory paralysis in patients who are susceptible to the drug, and embolism upon resumption of normal rhythm.

The maintenance of quinidine concentration depends on two definite factors: the dosage, and the rapidity of its excretion. Since quinidine is rapidly excreted and shows very slight cumulation, the element of importance in dosage is the size and frequency of the individual dose, rather than the total quantity given over a period of time.

1. *Dosage Factor.*—Although the average dose of quinidine is from about 15 to 30 grains daily, there are several reports on the use of extremely large doses. Viko, Marvin, and White[5] gave daily doses up to 60 grains. Levine and Fulton[6] gave as much as 112 grains in twenty-four hours to one patient with ventricular tachycardia, and 36 grains daily, for months, to another. In Gold's case,[4] the dosage was gradually increased to the point of minor toxic effects. Altogether, the patient took a total of 38,456 grains (more than 75 ounces of quinidine sulfate), or an average of about 48 grains daily for 802 days. Jezer and Schwartz[7] gave a total of 312 grains over a period of nine days, in total daily doses ranging from 6 to 72 grains, for the treatment of auricular flutter. Temporary amblyopia and irregular return of the flutter were noted.

2. *Excretion Factor.*—Quinidine excretion is influenced by a number of factors: individual variation, diuresis, renal permeability for the urinary solids, and muscular effort. However, excretion of the drug is carried on largely through the urine. According to Wedd,[8] this varies in individual cases, but usually the drug cannot be detected fifteen hours after the single maximum therapeutic dose. From this, one may conclude that there is little danger from cumulative effects, and also that, for continuous administration, the interval between doses should not be too great. There are several experimental studies which show that quinidine is very rapidly excreted.[9, 10] Ordinarily, not more than six hours should elapse if any continuous effect is desired.

Wiechman[11] found that, although individual differences in excretion occurred, in general, quinidine excretion was directly proportional to the urinary output. A greater amount was excreted on the day after the administration of small fractional doses than on the day after the same quantity was given as a single dose. Excretion was uninfluenced by digitalis therapy.

Weisman[12] studied the rate of concentration and elimination of quinidine, and found that single doses of 100 mg. (1½ gr.) produced a maximum concentration in the heart muscle in thirty minutes. It was completely eliminated from the heart in four hours. A single dose, six times as large, caused these periods to be doubled. The lungs, liver, kidney, and spleen reacted similarly. When four small doses were given at hourly intervals, the maximum concentration was reached in two hours and the drug disappeared in five hours.

CONCLUSIONS

1. Over a period of two and one-half days, 185 grains of quinidine were employed successfully in a case of unremitting ventricular tachycardia.

2. We have been unable to find any record of a larger dose of quinidine being given over a shorter period of time.

3. Safety in giving tremendous doses of quinidine over a short period of time in a case of intractable ventricular tachycardia is possible, providing an electrocardiographic study of the QRS interval is made before each dose of 10 grains. An increase of approximately 25 per cent is allowable in any lead. Above this, the danger of ventricular fibrillation increases, and further administration is unsafe.

4. The electrocardiographic studies and treatment were instituted, in this case, in the home, and could probably be employed with even greater ease in the hospital.

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Abstracts and Reviews

Selected Abstracts

Gregg, D. E., and Shipley, R. E.: Changes in Right and Left Coronary Artery Inflow With Cardiac Nerve Stimulation. Am. J. Physiol. 141: 382, 1944.

The effects of stimulation of the stellate ganglia and their cardiac branches on coronary inflow in the anesthetized, open-chest dog have been studied with the use of the rotameter (for recording mean rate of inflow) and the orifice meter (for recording phasic flow).

Stimulation of these structures usually causes a considerable and sustained augmentation of left coronary inflow and a somewhat smaller increase in right coronary inflow. In no instance was a sustained reduction in flow observed.

The increase in mean rate of flow is the resultant of a decreased inflow during systole and a proportionately larger increase in flow during diastole. Occasionally, the phasic redistribution of flow throughout the cycle is such that the net flow increase is quite small.

The augmentation of coronary inflow is frequently accompanied by simultaneous elevation of aortic blood pressure and/or heart rate. However, observations that the inflow increases when these variables either do not increase spontaneously or are artificially kept at the control level, indicate that these factors alone are not an indispensable part of the mechanism by which coronary inflow is increased.

The augmentation of coronary inflow is regarded as an indication of coronary vessel dilatation. The mechanism remains to be determined.

AUTHORS.

Langendorf, R., Katz, L. N., and Simon, A. J.: Reciprocal Beating Initiated by Ventricular Premature Systoles. Brit. Heart J. 6: 13, 1944.

A case is presented showing sinus rhythm and ventricular premature systoles followed at a fixed interval by another premature ventricular complex of supraventricular origin. The occasional presence of inverted P waves between the two premature ventricular beats suggested reciprocal rhythm. This was substantiated not only by the constant interval between the two premature ventricular beats but also by the occurrence of P waves preceding the second premature ventricular beat at a distance so short as to preclude the possibility of conduction of an impulse from the auricles to the ventricles in the second beat.

In the authors' case, evidence is presented to suggest that the point of re-entry was below the auricles and above the bifurcation of the common bundle, presumably within the A-V node.

It is pointed out that the retrograde P waves, in cases of reciprocal rhythm due to re-entry of retrograde impulses, merely indicate the presence of retrograde conduction, without in themselves constituting an essential part of the mechanism underlying reciprocal rhythm.

The various possibilities of interference, in the authors' case, between the sinus impulse and retrograde impulses causing reciprocal rhythm, are evaluated and instances of each cited.

The authors' case indicates that instances of fixed coupling of premature ventricular beats, even in the absence of P waves, indicative of retrograde conduction, may be examples of re-entry.

<div align="right">AUTHORS.</div>

Lawrence, J. S., and Forbes, G. W.: Paroxysmal Heart Block and Ventricular Standstill. Brit. Heart J. 6: 53, 1944.

A case is described showing periods of intermittent heart block and, occasionally, a phasic ventricular standstill. Conduction was normal in the intervening stages.

Eighteen reported cases of this type are reviewed.

It is suggested that arterial spasm or partial arterial occlusion is the main factor in the majority of these cases.

It was found possible to control the attacks by inhalations of amyl nitrite.

<div align="right">AUTHORS.</div>

Duras, P. F.: Heart Block With Aneurysm of the Aortic Sinus. Brit. Heart J. 6: 61, 1944.

A case is reported with an aneurysm of a sinus of Valsalva and complete heart block. The possible causes of the block are discussed, and the conclusion is drawn that the block was due to pressure of the aneurysm on the conducting path.

<div align="right">AUTHOR.</div>

Miller, R. A.: Auriculo-Ventricular Rhythm. Brit. Heart J. 6: 107, 1944.

This paper is based on observations on thirteen cases of auriculoventricular rhythm, the salient features of which have been correlated with appropriate facts recorded by others. The outstanding features fall under four headings as follows:

Physical exercise may now be added to the factors that precipitate A-V rhythm. Atropine can produce the rhythm disorder when a tachycardia is present, or when the heart rate is increasing. From these observations, it was decided that atropine acted simultaneously and unequally upon the sinoauricular node and the auriculoventricular node in order to produce A-V rhythm.

As a rule, the onset of A-V rhythm cannot be detected by the patient or the physician. Sometimes, however, the patient may complain of giddiness, weakness, or palpitation, and the doctor may note an abrupt fall in the pulse rate. An explanation for these symptoms and signs has been given.

Should A-V rhythm be complicated by ventricular bigeminy, it is generally transitory, but it may be intermittent for months, the onset of bigeminy being partially determined by the length of the Q-P interval, and by the site of origin of the ventricular contraction. It should be noted, however, that the critical Q-P interval, below which ventricular bigeminy ceases to appear, varies with the rate of the heart.

The prognosis for people with A-V rhythm is influenced and controlled by systemic disturbances and cardiac disease. The detection of the latter is sometimes possible by utilizing the following tests: vagal pressure, exercise, and atropine, provided such tests are performed and interpreted cautiously. These tests are only warranted when the etiology of A-V rhythm is obscure. Six such cases have been reviewed. One proved to be due to organic disease and the others to vagal dysfunction. In the former there was no deterioration in health over a period of one year, although the disorder persisted for this period. In those people with abnormal vagal tones as the etiological factor, it is probably possible to lead an active life for twenty-five years with intermittent A-V rhythm.

<div align="right">AUTHOR.</div>

Holford, J. M.: Unusual Electrocardiogram in Dextrocardia. Brit. Heart J. 6: 105, 1944.

The case here described was found in the course of a mass radiographic survey.

Radiography showed a heart in the position of complete dextrocardia, but otherwise of normal contour. The lung fields were clear. The left dome of the diaphragm was raised. The liver and stomach were not transposed.

In Lead I, P is upright, the QRS complex shows a downward deflection followed by an upward one of approximately equal magnitude, and T is shallow and diphasic. All the remaining leads appear normal.

AUTHOR.

Saphir, O., Wile, S. A., and Reingold, I. M.: Myocarditis in Children. Am. J. Dis. Child. 67: 294, 1944.

In 1,420 autopsies on children between the ages of 8 days and 16 years, ninety-seven instances of myocarditis were observed, an incidence of 6.83 per cent. This disease was encountered 150 times in 3,712 autopsies performed on adults during the same period, an incidence of 4.05 per cent. These figures represent myocarditis seen in a general pediatric hospital. Types of myocarditis occurring during the course of contagious diseases are not included; references to these, however, are made in the discussion.

Among the 97 cases of myocarditis, there was 1 in which the condition was diagnosed as postdiphtheritic inflammation of the myocardium. Myocarditis was associated with meningitis in 4 cases, with poliomyelitis in 7, with bronchopneumonia in 12, with lobar pneumonia in 3, and with nephritis in 3. Abscesses in the myocardium, associated with various infectious diseases and various portals of entry, were present in 16 instances. Myocarditis associated with bacterial endocarditis was present 5 times; myocarditis associated with subacute bacterial endocarditis 7 times. There were 13 instances of a "rheumatic type" of myocarditis. Rheumatic myocarditis was present 19 times, isolated myocarditis 3 times, and myocarditis in tuberculosis 4 times.

Fetal myocarditis, with the exception of myocarditis in congenital syphilis, if it occurs at all is extremely rare. The essential myocardial lesion in diphtheria is parenchymatous hyaline degeneration or necrosis. Later there occurs a reparative inflammatory process. It is questionable whether the latter should be considered true myocarditis. Myocarditis in measles is rarely encountered; nor does myocarditis occur frequently in mumps, whooping cough, smallpox, or varicella. It seems that inflammatory myocardial damage occurs much more often in scarlet fever than has been heretofore believed. Perhaps a parallel statement would be true for a number of other contagious diseases if further studies were made of the myocardium in such conditions. Myocarditis is also observed in epidemic meningitis and poliomyelitis. In the latter disease it seems to occur more frequently than is generally accepted. In bronchopneumonia and lobar pneumonia it is occasionally encountered. In pyemia, abscesses of the myocardium occur relatively frequently; however, a cursory examination of the myocardium often fails to disclose small abscesses.

Isolated myocarditis occasionally occurs in children who have no other disease that may be considered as the source of the myocarditis. Occasionally this form of myocarditis has been found associated with exanthematous diseases. It may cause sudden death in children who had been apparently healthy and in whom progressive myocardial weakness developed, more or less quickly. Anatomically it does not vary in histologic details from myocarditis in acute infectious diseases.

Myocarditis in bacterial and subacute bacterial endocarditis is often encountered, and rarely diagnosed, clinically. In rheumatic endocarditis and the "rheu-

matic type'' of endocarditis, myocarditis occurs frequently. This is the only type of myocarditis recognized and diagnosed clinically with any degree of frequency.

Miliary tubercles are found only occasionally in cardiac muscle. There is a type of myocarditis which occurs in tuberculosis without the formation of the typical granulation tissue. It is evident that this nonspecific myocarditis cannot be called tuberculosis. In the older literature, miliary gummas and gummatous myocarditis are reported to occur in infants with congenital syphilis. At present they seem to be encountered rarely.

Myocardial damage in uremia is rare, and may be explained by an extension of uremic pericarditis into the adjacent myocardium. Whatever may have caused the nephritis may cause the myocarditis. Myocarditis in trichinosis, blastomycosis and virus, rickettsial, and various other diseases is also mentioned.

Clinically, myocarditis may be suspected if, during the course of an infectious disease, a child suddenly becomes worse and begins to fail without apparent cause. Tachycardia out of proportion to the temperature, particularly if accompanied by cyanosis, is an early sign that may direct attention to the myocardium. Cardiac enlargement is frequently present, and the blood pressure is usually low. The electrocardiogram sometimes reveals significant changes.

In ninety-seven instances of myocarditis evidence of heart failure was noted thirty-two times. In the vast majority of these cases a diagnosis of rheumatic heart disease was made. Sudden death of patients with myocarditis was not unusual; nine out of sixty children died suddenly.

From our study it is evident that myocardial damage in children may and does occur in diseases other than rheumatic fever and diphtheria. The incidence of myocarditis in our series (6.83 per cent) indicates clearly that the possible occurrence of myocarditis during the course of an infectious disease must be borne in mind. The possibility of myocarditis having once been considered, further investigation may reveal additional confirmatory evidence. Perhaps the relatively high incidence of the clinical diagnosis of myocarditis for patients with rheumatic heart disease can be explained by the fact that it is generally accepted that myocarditis often occurs in patients with rheumatic heart disease.

The incidence of myocarditis as determined by routine examination of the heart is seemingly low. However, we suspect, especially from our experience with myocarditis in poliomyelitis, that myocarditis in general would be found frequently and would no longer be regarded as a rare condition if the myocardium were carefully examined histologically for the purpose of ruling out, or substantiating the presence of, inflammatory disease.

AUTHORS.

Krost, G. N.: Rheumatic Pericarditis With Effusion in Patients Under Two Years of Age. J. Pediat. 24: 514, 1944.

Pericarditis with effusion in two patients below the age of 2 years is reported as being of rheumatic etiology.

AUTHOR.

Hench, P. S., and Rosenberg, E. F.: Palindromic Rheumatism. Arch. Int. Med. 73: 293, 1944.

The authors describe an unusual, oft recurring disease of joints and adjacent tissues, thirty-four cases of which have been studied in the arthritic service of the Mayo Clinic since 1928. Its outstanding features are multiple afebrile attacks of acute arthritis and periarthritis, and sometimes also of para-arthritis, with pain, swelling, redness, and disability generally of only one, but sometimes of more than one, small or large joint, in an adult of either sex. The attacks appear suddenly and develop rapidly. They generally last only a few hours or days and

then disappear completely, but they recur repeatedly at short or long, *irregularly* spaced intervals. Despite the frequent recurrences and the transitory presence (in some cases at least) of an acute or subacute inflammatory polymorphonuclear exudate in the articular tissues and cavity, little or no constitutional reaction or abnormality is revealed by laboratory tests, and no significant functional, pathologic or roentgenographic residues occur even after years of disease and scores of attacks.

Since the most obvious and characteristic features of the condition described are its frequent recurrences, its attacks and retreats, the term "palindromic" seems fitting and descriptive, and is proposed by the authors for this specific condition.

Six typical cases are described in detail. There is a full discussion of the symptoms, signs, and laboratory findings.

<div align="right">AUTHORS.</div>

MacKeith, R.: Adrenal-Sympathetic Syndrome. Brit. Heart J. 6: 1, 1944.

Two cases of adrenal-sympathetic syndrome due to pheochromocytoma (chromaffin tissue tumor in the adrenal medulla) are described.

The first is unusual in that, though the patient had minor attacks almost daily for four years, there was only one major attack, which led to a diagnosis and operation, with cessation of the attacks.

The syndrome of chromaffin tissue tumors is reviewed. It is noted that, while many cases show widespread symptoms, others show only local symptoms, though the vasoconstriction is generalized. Paroxysmal hypertension is the one sign common to all attacks. The treatment is removal of the tumor.

<div align="right">AUTHOR.</div>

Hiller, G. A., and Johnson, R. M.: Abdominal Aortic Aneurysm. Rupture Into the Jejunum Preceded by Occult Blood in the Stool. Am. J. M. Sc. 207: 600, 1944.

A case of arteriosclerotic aneurysm of the abdominal aorta with rupture and perforation into the jejunum is reported.

Aneurysm of the abdominal aorta with pressure on the small bowel is a rare cause of blood in the stool.

<div align="right">AUTHORS.</div>

Naide, M., and Saijen, A.: A Test for Vascular Tone in Human Beings and Its Application to the Study of Vascular Diseases With Special Reference to the Etiology and Prevention of Thrombophlebitis. Am. J. M. Sc. 207: 606, 1944.

A clinical method for the determination of "vascular tone" in humans is described.

Results of vascular tone typing, carried out on 172 individuals, have revealed the wide range of vascular tone in normal persons and patients, and its significant role in the etiology and course of certain vascular diseases and in the selection of appropriate therapy.

The importance of vasospasm in initiating thrombophlebitis or phlebothrombosis has been disclosed by the test.

This test can indicate whether vasoconstriction and vasodilatation in different individuals are taking place in large or small vessels.

The relation of vascular tone to basal metabolic rate, blood volume, blood pressure, cardiac rate, heat elimination, emotional stimuli, and size of the pupil have been studied and discussed.

<div align="right">AUTHORS.</div>

Master, A. M., Nuzie, S., Brown, R. C., and Parker, R. C., Jr.:   The Electro-
cardiogram and the ''Two-Step'' Exercise.   A Test of Cardiac Function and
Coronary Insufficiency.   Am. J. M. Sc. 207: 435, 1944.

An experience gained over many years has proved the practical value of the
''electrocardiogram following the two-step exercise'' in three ways: First, the
blood pressure and pulse response indicate circulatory fitness by a standardized
measurement of vasomotor response.   Second, the ECG, changes are an indication
of the oxygen supply of the heart muscle itself.   Third, the control ECG reveals
the presence of arrythmias and is an indication of the condition of the myocardium
with the patient at rest.

The test is of importance in differentaiting functional from organic heart dis-
ease, particularly when physical examination, roentgen-ray film, fluoroscopy, and
ECG are negative.

Positive changes in the ECG after the ''two-step'' exercise indicate anoxemia of
the heart muscle or coronary insufficiency.   Both this test and the 10 per cent
oxygen anoxemia test were performed on every person considered in this report.
The ECG changes corresponded almost exactly in both tests.

The exercise must be standardized for age and weight since changes occur in
normal people if the effort is excessive.   Tables giving the number of trips to be
performed by normals have been published.   In normal persons, the blood pressure
and pulse return to within 10 points of resting levels in one and one-half minutes.
The following changes in the ''electrocardiogram after the two-step'' are considered
abnormal: A depression of the RST segment of more than 0.5 mm. in any lead,
a change from an upright T wave to an isoelectric (flat) or inverted T wave or
T-wave changes in the opposite direction.

In patients with coronary heart disease the test is of particular value in detect-
ing coronary insufficiency when it is latent.

In valvular heart disease, the test discloses the state of cardiac function, and
whether the cardiac output is adequate for the coronary arteries.

In patients with hypertension, the control ECG often shows evidence of coronary
insufficiency and, therefore, may not change after exercise.   There is a lag in return
of the blood pressure and pulse following the ''two-step'' exercise in effort syn-
drome (neurocirculatory asthenia), and the ECG gives evidence of anoxemia of the
heart muscle following exercise.   In this syndrome we believe there is a congenitally
small, hypoplastic heart which is inadequate on effort.

In chest deformities and in congenital heart disease the ''electrocardiogram after
the two-step'' is valuable.

An upper respiratory infection, lung disease, gastroenteritis, fatigue and lack
of sleep may produce abnormal results.

The ''electrocardiogram after the two-step'' is a short, harmless and practical
test.   It is suggested that it should be a routine procedure in men over 40 years
of age in the military service, and also for eliminating the unfit for special services
where unusual physical and mental strain are experienced, as in aviation, sub-
marine, raider forces, and so on.

                                                            AUTHORS.

La Due, J. S.:   The Role of Congestive Heart Failure in the Production of the
Edema of Acute Glomerulonephritis.   Ann. Int. Med. 20: 405, 1944.

The edema of twelve patients with acute glomerulonephritis was found to be
associated with right heart failure, as indicated, in every instance, by an elevated
venous pressure and cardiac dilatation.

In nine patients, most of the symptoms of congestive heart failure were pres-
ent, but, in three patients, the presence of peripheral edema was the only symptom

suggesting heart failure. More careful study of these three patients disclosed cardiac dilatation and elevated venous pressure.

The importance of hypertension in the pathogenesis of and relief of the congestive heart failure which frequently complicates acute glomerulonephritis has been emphasized. The earliest objective evidence of improvement of the heart failure in seven of eight patients not given digitalis was a fall in blood pressure; the return to normal of the venous pressure, and the disappearance of edema occurred slightly later.

There was a significant decrease in the diastolic heart volume of these patients after compensation had been established. This decrease was even greater two to four weeks after congestive failure had disappeared. The circulation time was normal or low in eleven of twelve patients studied, despite an elevation of the venous pressure. The pulmonic second heart sound was accentuated in eleven of twelve patients, suggesting the possibility of pulmonary hypertension.

<div style="text-align: right">AUTHOR.</div>

Altschule, M. D., and Zamcheck, N.: The Effects of Pleural Effusion on Respiration and Circulation in Man. J. Clin. Investigation 23: 325, 1944.

The effects of pleural effusion have been estimated in eight patients by comparison of measurements of the lung volume and the respiratory and cardiovascular dynamics before and after thoracentesis.

Atelectasis, decreased expansibility of the lungs, decreased negativity of intrapleural pressure, and shallow respiration are consequences of pleural effusion; anoxia may occur.

Increased peripheral venous pressure, a manifestation of impaired venous return consequent to changes in intrapleural pressure, is caused by pleural effusion. There are no changes in cardiac output or circulation time, at least at rest, as a consequence of pleural fluid.

It is concluded that pleural effusion impairs respiration and circulation in many ways, thereby favoring the occurrence of dyspnea and orthopnea; these symptoms will be most severe in patients who have extensive, diffuse disease of the lungs in addition to the effusion.

<div style="text-align: right">AUTHORS.</div>

Ryder, H. W., Molle, W. E., and Ferris, E. B., Jr.: The Influence of the Collapsibility of Veins on Venous Pressure, Including a New Procedure for Measuring Tissue Pressure. J. Clin. Investigation 23: 333, 1944.

When arm veins are distended, the venous pressure measures central influences, and is independent of the local pressure around the veins.

When arm veins are collapsed, the venous pressure measures the tissue pressure that has collapsed them, and is independent of central influences.

The measurement of local venous pressure in freely collapsed veins offers a means of measuring tissue pressure under conditions of equilibrium.

<div style="text-align: right">AUTHORS.</div>

Schott, A.: Circulatory Failure Due to Vitamin B Deficiency. Brit. Heart J. 6: 27, 1944.

Three cases of circulatory disturbances due to vitamin B_1 deficiency are described with special reference to some unusual clinical and electrocardiographic features. Two of the three patients took an excessive amount of alcohol, in the third case the condition was caused by deficient diet only. All responded to treatment with vitamin B_1.

<div style="text-align: right">AUTHOR.</div>

Holman, E.: Further Observations on Surgery of the Large Arteries. Surg., Gynec. & Obst. 78: 275, 1944.

The author describes the surgical principles and technique involved in surgery of the large arteries. He also summarizes and discusses these principles.

While the discussion is largely one of surgical technique, it should be of interest to cardiologists as well, who must both make the diagnosis of cases suitable for such operations, as well as follow them afterward.

<div align="right">McCulloch.</div>

Homans, J.: Deep Quiet Venous Thrombosis in the Lower Limb. Surg., Gynec. & Obst. 79: 70, 1944.

Thrombosis of a quiet type (phlebothrombosis), commencing in the deep veins below the knee, is the source of most nonobstructive processes threatening pulmonary embolism as well as most obstructive inflammatory ones responsible for painful swelling of the whole lower limb (thrombophlebitis).

Thrombophlebitis of the fully obstructive type presents no satisfactory indication for operations, but rather for release of the associated vasoconstriction by lumbar sympathetic block.

It is desirable, and usually possible, to distinguish an early stage of quiet, deep, venous thrombosis, when the process is still confined to the lower leg or has given rise to an unattached propagating thrombus in the popliteal and femoral veins, threatening pulmonary embolism. The signs of such a state are discussed and the clear indication for femoral interruption, to forestall or stop embolism and prevent the development of phlegmasia alba dolens, is pointed out.

An advanced stage of quiet, deep, venous thrombosis, more or less adherent but not obstructive, can also be distinguished. Its signs are discussed. Thrombosis will often have propagated above the inguinal ligament into the external and, occasionally, especially on the left, the common iliac vein. With such a process, thrombosis of the deep veins among the muscles of the thigh (profunda femoris system) is usually associated. Thrombosis in these deep veins may even be present when no thrombus is found on exploration of the superficial femoral vein below the profunda.

The advantages of interruption of the common iliac vein, for all such advanced, quiet, venous thromboses, are discussed, and the operative procedure, for both the right and left limbs, is described.

Some observations upon interruption of the vena cava are made.

<div align="right">Author.</div>

Suarez, J. R. E., Taquini, A. C., and Fasciolo, J. C.: Action of Atropine on the Minute Volume of the Heart. Rev. argent. de cardiol. 10: 291, 1943.

The subcutaneous administration of 1 mg. atropine increased cardiac minute volume in six of the eight subjects studied. Pulmonary ventilation and oxygen consumption increased slightly in the majority of cases. In every instance, the heart rate increased in greater proportion than the minute volume.

As a result of the changes in minute volume, pulmonary ventilation, oxygen consumption, and heart rate, the following changes occurred in the majority of cases: decrease of the arteriovenous difference, of the CO_2 of expired air, of the respiratory quotient, and of the cardiac output, and increase of the ventilation equivalents for O_2 and CO_2.

The circulatory changes produced by atropine cannot be explained solely by the increase of heart rate and oxygen consumption.

<div align="right">Authors.</div>

Book Review

HIPERTENSION ARTERIAL NEFROGENA: By Eduardo Braun-Menéndez, Juan Carlos Fasciolo, Luis F. Leloir, Juan M. Muñoz, and Alberto C. Taquini, Libreria y Editorial ''El Ateneo,'' Buenos Aires, 1943, 462 pages, 93 figures.

This book is the result of the cooperative effort of a research team at the Institute of Physiology of Buenos Aires.   In the preface, Professor B. A. Houssay* states that these men are his former co-workers, and a good part of the work recorded in this book was done under his direction.   A glance through the index reveals the wide scope of the book and the emphasis placed on experimental work. Clinical and therapeutic problems, however, are not overlooked.

The first chapter reviews different experimental methods of producing permanent hypertension.   The second deals with a functional and pathologic study of the hypertensive animal.   Next comes a discussion of neurogenic and humoral factors in the production of hypertension, with a study of the pressor substance excreted by the ischemic kidney.

The fourth chapter describes renin, its general properties and method of preparation, and the type of reaction between it and components of the blood.   Methods of assay, specificity, and different actions of renin are further described.

A brief paragraph deals with the origin, properties, preparation, and actions of hypertensinogen (prehypertensin, renin activator).   The following chapter is devoted to hypertensin (angiotonin).   Methods of preparation and assay, and pharmacologic action on vessels, heart, kidney, respiratory center, metabolism, and smooth muscle are described; clinical effects are also reported.   Angiotonin is described as a ''pressor and vasoconstrictor substance due to interaction of renin and renin activator.   It is probably a low molecular weight polypeptide.   It is a dializable, thermostable, acid stable, alkali labile substance, soluble in water, insoluble in most organic solvents, easily destroyed by proteolytic enzymes.'' ''Its action is of the musculotropic type, being unaffected by either cocaine, ergotamine, or Fourneau, being increased by veritol and tyramine.''

Chapter 7 deals with hypertensinase (angiotonin inhibitor), and Chapter 8 with the formation, secretion, and destruction of renin in the body.   The protective action of a normal kidney, the influence of endocrine glands and of pregnancy, and different vasoconstrictor substances are further studied.

The following six chapters deal with human hypertension.   Chapter 16 discusses the medical treatment of nephrogenic hypertension, and Chapter 17, the surgical treatment.   The last chapter compares experimental and human hypertension.

An interesting appendix on methods and technique closes the book.   The bibliography comprises more than 1,100 references.

This important monograph contains the latest contributions to the subject of experimental hypertension, and reviews the subject from a well-balanced and objective point of view.   It will be essential for experimental workers, and may prove better than many books on the clinical aspects of hypertension.

ALDO LUISADA.

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*Professor Houssay has been working for the Rockefeller Foundation since his dismissal by the present governmental regime of Argentina.

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Original Communications

THE Q_1 DEFLECTION OF THE ELECTROCARDIOGRAM IN
BUNDLE BRANCH BLOCK AND AXIS DEVIATION

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IT IS the purpose of this article to present and discuss observations on the incidence, in standard Lead I, of QRS complexes which display an initial downward deflection, or Q wave.

At the beginning of this study, we examined the tracings taken in 169 cases of bundle branch block. In all of these, the QRS interval measured 0.12 second, or more, and pronounced slurring or notching of the broadest QRS component was present. In 92 cases, there was no S wave in Lead I; these were classified as left branch block. The remaining 77 cases, in which there was a conspicuous S deflection in Lead I, were considered characteristic of right branch block. In 84, or 91.3 per cent, of the cases of left branch block, the first and only QRS component in Lead I was a broad R wave; in the remaining 8 cases (8.7 per cent), a small initial downstroke preceded this deflection (Table I). In the same group of cases, there were 33, or 35.9 per cent, in which the QRS complex of Lead III began with a downstroke, and these included one of the 8 which displayed a Q wave in Lead I. A Q_1 deflection was present in 34, or 44.2 per cent, and absent in 43, or 55.9 per cent, of the cases of right branch block. The QRS complex of Lead III began with a downstroke in 36.4 per cent of the cases of this group.

These observations on the incidence of Q_1 in bundle branch block were confirmed by examination of the tracings obtained in a group of cases of bundle branch block in which the conduction defect was present on one examination, but absent on an earlier or later occasion.

TABLE I

THE FREQUENCY OF Q_1 AND Q_3 IN THE ELECTROCARDIOGRAMS OF 169 PATIENTS WITH BUNDLE BRANCH BLOCK

| | LEFT BUNDLE BRANCH BLOCK | | RIGHT BUNDLE BRANCH BLOCK | |
	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE
Q_1 present	8	8.7	34	44.2
Q_1 absent	84	91.3	43	55.9
Q_3 present	33	35.9	28	36.4
Q_3 absent	58	64.1	49	63.6
Q_1 and Q_3 present	1	1.1	11	14.3
Q_1 and Q_3 absent	52	56.5	26	33.8
Total	92		77	

TABLE II

THE EFFECT OF DEVELOPMENT OF BUNDLE BRANCH BLOCK ON THE Q WAVE IN LEAD I IN 102 PATIENTS SHOWING, AT ONE TIME, BUNDLE BRANCH BLOCK, AND, AT ANOTHER, NORMAL CONDUCTION

| | LEFT BUNDLE BRANCH BLOCK | | RIGHT BUNDLE BRANCH BLOCK | |
	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE
Q_1 present. Normal conduction	20	25.3	8	34.8
Q_1 absent. Normal conduction	59	74.7	15	65.2
Q_1 present. Bundle branch block	4	5.1	8	34.8
Q_1 absent. Bundle branch block	75	94.9	15	65.2
Q_1 absent, with and without block	57	72.1	14	60.9
Q_1 disappeared, with block	18	22.8 (of total) 90.0 (of those with Q_1)	1	4.3 (of total) 12.5 (of those with Q_1)
Q_1 appeared, with block	2	2.5 (of total) 3.4 (of those without Q_1)	1	4.3 (of total) 6.6 (of those without Q_1)
Q_1 with and without block	2	2.5 (of total) 10.0 (of those with Q_1)	7	30.4 (of total) 87.5 (of those with Q_1)
Total	79		23	

In our own files, we found 9 cases of this kind in which the block was on the left side, and 10 cases in which it was on the right side. By searching the literature, we collected 70 additional cases of the first sort and 13 of the second.[1-55] We did not include in this series any cases of the Wolff-Parkinson-White syndrome, nor any cases in which the QRS interval measured less than 0.12 second when the block was present, or more than 0.10 when it was absent. The incidence of Q_1 and other data relating to the 79 cases of left and 23 cases of right branch block assembled in this way are given in Table II. In 20 of the 79 cases of the first group, the QRS complex of Lead I began with a downstroke when intraventricular conduction was normal, and in all but two of these it began with an upstroke when left branch block was

TABLE III

INCIDENCE OF Q_1 IN PATIENTS WITH LEFT BUNDLE BRANCH BLOCK, RIGHT BUNDLE BRANCH BLOCK, LEFT AXIS DEVIATION, AND RIGHT AXIS DEVIATION

	LEFT BUNDLE BRANCH BLOCK		RIGHT BUNDLE BRANCH BLOCK		LEFT AXIS DEVIATION		RIGHT AXIS DEVIATION	
	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE
Q_1 present	13	7.3	41	41	175	58.3	6	6
Q_1 absent	164	92.7	59	59	125	41.7	94	94
Total	177		100		300		100	

TABLE IV

Q_1 RELATIONSHIPS IN PATIENTS WITH LEFT BUNDLE BRANCH BLOCK AND LEFT AXIS DEVIATION (CONSECUTIVE CASES)

TYPE OF ELECTROCARDIOGRAM	Q_1 PRESENT	Q_1 ABSENT	TOTAL
Left axis deviation			
Index 24 or less	51	49	100
Index 25 or more	62	38	100
Normal T waves	69	31	100
Inverted T_1 or T_1 and T_2	55	45	100
Questionable left bundle branch block (QRS = 0.10 to 0.12)	46 (42.6%)	62 (57.4%)	108
Left bundle branch block	8 (8.7%)	84 (91.3%)	92

present. In the other 59 cases, the QRS complex of Lead I began with an upstroke when intraventricular conduction was normal; in 2 of these it displayed a Q wave when the left limb of the His bundle was blocked. As in the cases of left bundle branch block previously analyzed, the incidence of a Q_1 deflection was very low; it occurred in the presence of block in only 4 cases, or 5.1 per cent of the group. There was a Q_1 deflection with normal intraventricular conduction in 8 of the 23 cases of the second group, which is rather small for statistical purposes; in 7 of these, this deflection was likewise present when the right bundle branch failed to conduct. In the remaining 15 cases, Q_1 was absent with normal intraventricular conduction; in one of these, this deflection appeared when the right branch of the bundle was blocked.

The foregoing observations led us to compare the incidence of Q_1 in simple axis deviation with its incidence in bundle branch block. The ventricular complexes which depict simple left axis deviation and those which represent left branch block are often very similar in general contour, but our observations indicate that the electrocardiographic changes in these two conditions are fundamentally different in origin (Table III). With regard to the incidence of Q_1, left branch block is very different from simple left axis deviation (Table III). The relatively great frequency of a conspicuous Q_1 in simple left axis deviation, as compared to left branch block, is not materially affected by the criteria employed in the selection of examples of the former (Table IV). A Q_1 deflection was present in 51 of 100 cases of simple

TABLE V

Q-WAVE RELATIONSHIPS IN PATIENTS WITH RIGHT BUNDLE BRANCH BLOCK AND RIGHT AXIS DEVIATION

TYPE OF ELECTRO-CARDIOGRAM	Q_1 PRESENT		Q_3 PRESENT		Q_1 AND Q_3 PRESENT		NO Q		TOTAL
	NUM-BER	PER-CENT-AGE	NUM-BER	PER-CENT-AGE	NUM-BER	PER-CENT-AGE	NUM-BER	PER-CENT-AGE	
Right axis deviation	6	6.0	81	81.0	2	2.0	15	15.0	100
Right bundle branch block	34	44.2	28	36.4	11	14.3	26	33.8	77

left axis deviation in which the axis deviation index $(R_1 + S_3) - (R_3 + S_1)$, was 24 or less, and in 62 of 100 cases of left axis deviation in which this index exceeded 24. This deflection was present in 69 of a series of 100 consecutive cases of simple left axis deviation with normal T waves, and in 55 of 100 consecutive cases of the same kind in which the T waves were inverted in Lead I or in Leads I and II. It is of particular interest that Q_1 was present in 42.6 per cent of a series of 108 cases, all that could be found in a file of 8,000 electrocardiograms, in which definite left axis deviation was associated with a QRS interval of 0.10 to 0.12 second. With respect to the incidence of this deflection, electrocardiograms of this kind resemble those which depict simple left axis deviation. and are quite unlike those which represent left bundle branch block.

In simple right axis deviation, the frequency of Q_1 is very small, about the same as in left branch block, whereas, in right branch block, the frequency of this deflection is not very different from its frequency in left axis deviation (Tables I and V). The incidence of Q_3 is very high in right axis deviation and relatively low in right bundle branch block.

DISCUSSION

The incidence of Q_1 in bundle branch block has received little attention in the literature. Many years ago. Willius[56] recorded the size of the different QRS components in 99 examples of left branch block. His tables show that Q_1 was present in only two of his cases. but he did not comment upon this infrequency. In 1916, Lewis[57] was under the impression that Q_1 was usually present in bundle branch block of the common type; in 1924 he spoke of it as appearing to a variable extent.[58] In 1931, Wilson. Macleod. and Barker[59] stated that, in left branch block. Q is almost always present in Lead I and absent in Lead III. This statement was evidently based upon an impression, rather than upon the examination of an adequate series of cases.

With regard to the frequency of a Q_3 deflection, the curves that represent canine branch block are quite different from those that represent human branch block. In 6 of Lewis' experiments on dogs, Q_3 became larger; in two, it disappeared; and, in one, it persisted un-

changed when the left bundle branch was cut. In the remainder, it was absent both before and after section of this tract. A Q_1 deflection was present in four and absent in two of six examples of canine left branch block studied by Wilson and Herrmann.[60]

The rarity of Q_1 in human left branch block and the pronounced tendency for this deflection to disappear when left branch block develops clearly indicate that, in the vast majority of human electrocardiograms, it represents electrical forces originating in left ventricular muscle, or at least in muscle which receives the excitatory impulse by way of the left Purkinje plexus. The relatively high frequency of Q_1 in right branch block, and the tendency for this deflection to persist when normal conduction gives place to this disturbance, point in the same direction. Lewis, believing that the incidence of Q_1 was high in bundle branch block of the common type and, at the same time, that this kind of block was due to a conduction defect in the right bundle branch, arrived at the correct conclusion—that this deflection was contributed to the human bicardiogram by the levocardiogram. This is an instance in which the conclusion was valid even though the premises were erroneous.

Although it is clear that Q_1 usually represents electrical forces produced by the activation of left ventricular muscle, direct evidence as to the exact manner of its origin is not available. In experiments on dogs, endocardial readings have been employed in an attempt to locate the regions of ventricular muscle which are first to pass into the active state, but the data obtained in this way are of comparatively little value for the purpose of ascertaining the origin of the earliest QRS component of the human electrocardiogram. In the first place, the incidence of Q_1 is by no means the same in canine as in human curves, and, in the second, endocardial readings are not entirely trustworthy, as Wilson, Macleod, and Barker have pointed out. Even if the ventricular point which is activated earliest were known, we could not feel certain that Q_1 is written by events occurring in its neighborhood, for the electrical forces developed in this region may be overbalanced by the more rapid development of opposing forces somewhere else before they become large enough to produce a potential difference between the distant electrodes on the two arms.

The activation of left ventricular muscle may give rise to a Q_1 deflection by producing initial positivity of the right arm, initial negativity of the left arm, or both. In normal subjects, initial negativity of the anterolateral surface of the left ventricle often produces a Q deflection in leads from the left side of the precordium, and is frequently transmitted to the left arm as well. This negativity is transmitted to the epicardial surface from the ventricular cavity when the subendocardial muscle of the anterolateral wall enters the active state later, or produces electrical forces of less magnitude than the

subendocardial muscle on the opposite side of the left ventricle. It may, therefore, be ascribed to unbalanced forces produced by the spread of the excitatory impulse into the septum from the left Purkinje plexus. These same forces and, also, those generated by activation of the free wall of the right ventricle from within outward produce initial positivity of the epicardial surface on the right side of the heart, which gives rise to small R waves in leads from the right side of the precordium and is sometimes transmitted to the right arm. The absence of Q_1 in the vast majority of the cases of human left branch block appears, therefore, to be due to the absence of electrical forces normally produced by the activation of septal muscle from left to right.

What is the significance of Q_1 in the small percentage of cases of human left branch block in which it occurs? In left branch block, no left ventricular muscle is undergoing activation at the beginning of the QRS interval, and, if a Q deflection is present, it must be ascribed to forces of right ventricular origin. Under certain circumstances the initial positivity of the surface of the right ventricle due to the outward spread of the impulse through its free wall, which usually gives rise to small R waves in leads from the right side of the precordium in left branch block, may be transmitted to the right arm and thus give rise to a Q_1 deflection. It is apparent that this often happens in the dog and seldom happens in man. In the former, the long axis of the heart is much more nearly in line with the long axis of the body, and this may account for the difference in the frequency of Q_1 between canine and human left branch block. Rotation and elevation of the heart after section of the left bundle branch have caused a Q_1 deflection to appear in experiments on the dog, but not in experiments on the monkey, an animal in which the heart, with regard to its position, is more like that of man.[51] No peculiarities in the position of the heart were noted in the thirteen cases of left branch block in our series in which a Q_1 deflection was present. Both in the dog and in man, the presence of a Q_1 deflection, when the left branch of the His bundle is blocked, may, of course, depend upon some factor other than the position of the heart. A possibility that must be considered is that it is due to some peculiarity of the Purkinje system or the architecture of the subdivisions of the bundle branches, and consequently of the order of ventricular activation. In two instances, it was noted that a Q_1 deflection was present both before and after the development of left branch block, and had the same contour in both tracings. There exists, then, the possibility that in some instances the distribution of the conducting tracts is such as to lead to more rapid or earlier activation of those parts of the right ventricular muscle which produce forces of the kind that give rise to a Q_1 deflection, and that under these circumstances this deflection occurs and displays the same form in both bicardiogram and dextrocardiogram. This would account for the rare cases in which Q_1 disappears when right branch block develops.

In order to ascertain whether the presence of a Q_1 deflection in left bundle branch block has any diagnostic significance, we reviewed the histories of the thirteen patients in our own series and twenty-four cases found in the literature which presented this combination. An autopsy was performed in only two of our own cases. One of these was that of a man, aged 51 years, and in this instance the right coronary artery was occluded and the posterior ventricular wall was infarcted; the ventricular septum was not involved. In the second case, that of a man aged 56 years, there were pronounced cardiac hypertrophy, moderate coronary sclerosis, and slight fibrosis and patchy fatty degenerative infiltration of the myocardium. No macroscopic, circumscribed, septal lesions were found. In the remaining eleven cases, the following clinical diagnoses were made: arteriosclerotic heart disease with questionable coronary occlusion in two; coronary occlusion in five, in one of which left branch block antedated the symptoms pointing to infarction; arteriosclerotic heart disease with congestive failure in two; and rheumatic heart disease with mitral stenosis and aortic insufficiency in two.

The data relating to the conditions present in the twenty-four cases found in the literature are meager.[8, 22, 25, 32, 36, 41, 54, 56, 57, 62-70] In eight instances, no details of any kind were given as to the nature of the cardiac lesions. One patient had arteriosclerotic heart disease, cardiac enlargement, aortic insufficiency, and congestive failure. This patient died, but was not autopsied. Another had pericarditis with effusion and recovered; a third was said to have myocardial degeneration; a fourth, auricular fibrillation with congestive failure; a fifth, mitral stenosis; a sixth, aortic insufficiency; a seventh, diphtheria; an eighth, arteriosclerotic heart disease with failure. The ninth and tenth were reported as cases of coronary thrombosis in which the clinical diagnosis was confirmed by electrocardiographic examination; both of these patients recovered.

The remaining six patients died and were subjected to autopsy. The ventricular septum was involved in all. In one instance, there was occlusion of the anterior descending coronary artery, with infarction involving the anterior and part of the posterior wall of the left ventricle, the septum, and the apex. The interventricular septum was almost completely infarcted and in a state of liquefaction necrosis.[54] In another case there was thrombosis of an artery supplying the septum, with myocardial infarction and serofibrinous pericarditis.[66] In a third there was anterior infarction involving the septum.[32] The fourth was one with multiple infarcts; the lower, anterior part of the interventricular septum was involved.[70] In the fifth, described in the same report[70] as the fourth, a diagnosis of hypertensive heart disease with congestive failure was made, and moderate sclerosis of the coronary arteries was found post mortem. Histologic studies disclosed small scars in the myocardium, including a few in the septum, but the bulk

of the heart muscle appeared to be in good condition. In the sixth and last case,[63] the QRS interval measured only 0.107 second, but the precordial electrocardiogram indicated that activation of the left ventricle was delayed. At autopsy there was no cardiac hypertrophy; a healed infarct was found. It involved the entire apex, the apical four-fifths of the anterior and lateral walls of the left ventricle, and apical four-fifths of the anterior two-thirds of the interventricular septum.

From these few data, no very definite conclusions can be drawn. The heart was examined post mortem in only eight of the thirty-seven cases of left branch block with a Q, deflection which we were able to collect. It may be significant that, in six of these, myocardial infarction had occurred, and that, in five of the six and in one additional case, septal lesions were present. On the other hand, the cardiac abnormalities diagnosed clinically in many of the remaining twenty-nine cases in which there was no autopsy are not of a kind in which septal involvement would be expected. Even when bundle branch block is found after the occurrence of symptoms and physical signs characteristic of coronary thrombosis, one cannot feel certain that a large amount of the ordinary muscle of the ventricular septum has been infarcted. We know, however, that, in dogs, ligation of the septal artery, a large vessel not present in man, produces infarction of the basal part of the ventricular septum and often induces right bundle branch block or complete atrioventricular block.[71] Whether it ever induces left branch block alone is not certain. Right branch block produced in this way is sometimes, although not always, represented by ventricular complexes quite different in form from those obtained after section of the right branch of the His bundle.

On theoretical grounds, one might expect that, in left branch block, damage to the ventricular septum would lead to the appearance of a Q deflection in Lead I. In uncomplicated left branch block, the cavity of the right ventricle is negative throughout the QRS interval, but the cavity of the left is initially positive because of the direction of the electrical forces produced by activation of the septal muscle from right to left. This initial positivity is transmitted through the still inactive free wall of the left ventricle to the outer surface of this chamber and to the adjacent parts of the body, including the left side of the precordium, the left axilla, and, when the heart is in a relatively horizontal position, as in most patients with left branch block, to the left arm. Under these circumstances, the QRS complex of leads from the left side of the precordium display no Q deflection, and those of Lead I are of the same form. When the septum is extensively damaged, the electrical forces produced by its activation are reduced or abolished, and the initial negativity of the right ventricular cavity is transmitted to the left, and, consequently, to those regions on the left side of the body that are initially positive in left branch block when the septal

muscle is healthy. When this happens, Q deflections occur in leads from the left side of the precordium. They may be expected in Lead I also, although, in one case of this sort on record, large Q waves were present in leads from the left side of the precordium, but not in Lead I.[72]

From the data available, we cannot be sure that the mechanism in question gave rise to the Q_1 deflection in the cases of left branch block with septal lesions under consideration. In 2 of these, this deflection appeared after symptoms characteristic of coronary thrombosis had occurred, which suggests that infarction of the septum produced it. In another case, however, the Q_1 deflection antedated the coronary accident. The final decision as to whether there is a pronounced positive correlation between the presence of a Q_1 deflection in left branch block and septal involvement must wait until more extensive studies have been carried out. In the meantime, it is desirable that a full set of precordial leads be taken whenever a Q_1 deflection is encountered in tracings otherwise characteristic of left branch block, not only for the purpose of ascertaining whether left branch block is really present, but also to find out whether a Q deflection is present in leads from the left side of the precordium and left axilla.

It must be remembered that bundle branch block in man is almost always complicated by other cardiac abnormalities. The form of the electrocardiogram is determined not only by the failure of one bundle branch to conduct, but by extensive lesions of the ordinary ventricular muscle, as in infarction, and by involvement of other conducting tracts or the Purkinje network. Wilson and Herrmann[60] severed minor and major subdivisions of the left bundle branch in their experiments on dogs. In one instance, a cut on the left side of the septum, after the right branch of the His bundle had been divided, led to the appearance of a prominent Q_1 deflection. The possibility that the presence of Q_1 in left branch block is sometimes due to a combination of conduction defects must, therefore, be borne in mind.

The similarity in general contour between the ventricular electrocardiograms obtained in preponderant hypertrophy of the left ventricle and those characteristic of bundle branch block of the more common type has attracted attention for a great many years. Lewis, believing that the right branch of the His bundle was the one affected in bundle branch block of this type, brought forward a considerable body of evidence in support of the view that the ventricular complex was dominated by the levocardiogram in both conditions. Now that the block is known to be on the left side instead of the right, this view is no longer tenable.

The similarity in question involves the position of the mean electrical axis, the direction of rotation of the instantaneous electrical axis, the direction and sequence in time of the major QRS deflections of the different limb leads, and the form of the T waves, which are almost always inverted in Lead I in left bundle branch block and are very

often inverted in this lead in left ventricular hypertrophy. In many instances of great hypertrophy of the left ventricle, the QRS interval is increased to between 0.10 and 0.12 second, and, under such circumstances, it may be difficult to ascertain whether the electrocardiographic abnormalities are due to left ventricular hypertrophy alone or to incomplete left branch block.

Luten and Grove[25] and Hyman and Parsonnet[25] championed the view that pronounced left axis deviation with inversion of the T deflections in Lead I and upright T waves in Lead III is due to incomplete branch block, even when the QRS interval is not distinctly increased. Luten and Grove stressed the point that this conception was the only one that satisfactorily explained both the axis deviation and the form of the T waves. The anatomic arguments which they advanced to support it are no longer valid because they were based on the erroneous ideas concerning the diagnosis of right and left branch block which were current at the time their paper was written. In 1920, Fahr[12] put forward the hypothesis that the form of the ventricular complex in preponderant enlargement of the left ventricle is due to an increase in the length of the subdivisions of the left branch of the His bundle, and a consequent delay in the activation of the muscle of the left ventricle as compared to that of the right. At the same time he asserted that the classical views as to the location of the conduction defect in the two varieties of bundle branch block were erroneous, and that what had been considered right was really left branch block, and vice versa. Fahr's contention is clearly in accord with the observations of Luten and Grove and Hymen and Parsonnet, and supports the view that left axis deviation accompanied by inversion of the T waves in Lead I is the first stage, so to speak, in the development of left branch block; it also offers an alternative explanation of the tendency toward an increase in the QRS interval in left ventricular hypertrophy, attributed by Lewis to the increased thickness of the left ventricular wall.

The views regarding the cause of left axis deviation and inversion of the T deflections in Lead I in preponderant enlargement of the left ventricle held by Fahr are nearly, although not exactly, equivalent to the idea that these electrocardiographic changes are the result of incomplete left bundle branch block. Now, it is obvious that the initial QRS components in incomplete left branch block must be identical in form with those present in complete left branch block. In both cases these components represent the earliest phases of the dextrocardiogram, and there can be no reason why this should begin with a downward deflection in the one case and not in the other. It is for this reason that we have compared the incidence of Q_1 in axis deviation with its incidence in bundle branch block (Table IV). As we have already pointed out, this deflection is present in about one-half the cases of left axis deviation, and its frequency is nearly the same, regardless of whether we confine our attention to cases in which the

axis deviation index is very large or to cases in which it is only moderately increased, to cases in which the T waves are normal or to those in which the T waves are inverted in Lead I, or to cases in which the QRS interval lies within the accepted normal range or to those in which it measures between 0.10 and 0.12 second. On the other hand, Q_1 occurs in less than one-tenth of the cases of left bundle branch block. Contrary to what would be expected if left axis deviation were due to slow conduction of the cardiac impulse through the left limb of the His bundle, there is no tendency for the incidence of Q_1 to fall as the axis deviation index rises, or as the QRS interval lengthens. In order to obtain additional data bearing upon this problem, we reviewed all of the electrocardiograms taken in this laboratory over a period of three years with reference to the number of cases of left axis deviation in which Q_1 was the largest Q wave present in any of the limb leads; this information had been routinely coded. There were 1,199 cases of left axis deviation, and Q was largest in Lead I in 566, or 47.2 per cent of the total; Q was also largest in Lead I in 39 per cent of the 588 classified as showing slight left axis deviation, 54 per cent of the 611 classified as showing pronounced left axis deviation, and 40.4 per cent of 304 cases in which the T waves were inverted in Lead I and no digitalis had been given. In a review of curves of this last type, it was often noted, when a series of curves had been taken, that inversion of the T waves developed with the passage of time without any accompanying change in the contour of the QRS complex. These data show clearly that there is no justification for considering incomplete left branch block the sole, or even a common, cause of left axis deviation alone, or of left axis deviation associated with inversion of the T deflections in Lead I. For, if it were, we should certainly expect the incidence of Q_1 in left axis deviation to approach its incidence in complete left branch block as the form of the ventricular complex became more abnormal with respect to the value of the axis deviation index, the form of the T waves, or the length of the QRS interval.

We do not, of course, deny that left axis deviation, whether or not it is accompanied by inversion of T in Lead I, by an increase in the QRS interval, or by both, is sometimes due to incomplete left bundle branch block. When a Q deflection is present in Lead I, however, this is very unlikely, because the incidence of this deflection cannot be greater in incomplete than in complete left bundle branch block. When Q_1 is absent, the estimation of the probability that incomplete left branch block is or is not present is much more difficult. The probability that it is present is no doubt greater when the QRS interval measures between 0.10 and 0.12 second than when it is shorter. Since the incidence of Q_1 reached 42.6 per cent in the group of 108 cases of left axis deviation in which the QRS interval was more than 0.10 and less than 0.12 second in length and was no greater in those in which T_1 was inverted than in those in which it was upright, it seems prob-

able, however, that only a small percentage of the curves of this kind, in which Q_1 is absent, represent a conduction defect in the left limb of the His bundle.

In Lead III, the QRS complex begins with a downward deflection (Q or QS) in about one-third of the cases of left bundle branch block, and in approximately the same percentage of the cases of right branch block. In left branch block this deflection is not followed by a positive component, and should, therefore, be called QS instead of Q. Its presence may be due either to initial positivity of the left arm, to initial negativity of the left leg, or to both. The former is exceedingly common in left branch block because the initial positivity of the cavity of the left ventricle due to the spread of the cardiac impulse through the septal muscle from right to left is usually transmitted to the left arm. Were it not for the circumstance that the left leg is also initially positive in the majority of cases, because the initial positivity of the right ventricular surface due to the spread of the impulse through the free wall of the right ventricle is transmitted to it, a QS deflection would occur in Lead III almost as frequently as Q is absent in Lead I, and for the same reason. In a considerable percentage of the cases of left bundle branch block, the surface of the right ventricle is initially negative, as is shown by the absence of an R deflection in leads from the right side of the precordium, and in many of these this initial negativity is, no doubt, transmitted to the left leg and contributes to the frequency of a QS deflection in Lead III. It should be pointed out that these relations hold when the heart is in a relatively horizontal position. When the heart is relatively vertical, the potential of the left leg is like that at the left, instead of like that at the right, ventricular surface. In the dog, the long axis of the heart is nearly in line with the long axis of the trunk, and Q, or QS, deflections are very rare in Lead III in canine left branch block. In canine right branch block, on the other hand, Q_3 is present more often than absent.

In the kind of branch block curves that closely resemble those obtained in preponderant hypertrophy of the right ventricle with regard to the direction and relative size of the ventricular deflections of the standard limb leads, a Q_1 component very rarely occurs. Curves of this kind, which were at one time considered characteristic of left branch block, are very uncommon. In the great majority of the cases in which they occur, the precordial electrocardiogram is in every way typical of right branch block; in some instances, however, it indicates that the conduction defect is on the left side. Of the seventy-seven cases classified as right branch block in Table I, there were only seven in which the electrocardiograms were of this kind. In the other seventy cases, the QRS complex of Lead I displayed a narrow R wave which often attained a voltage equal to, or greater than, that of the broad, notched, or slurred S wave which followed it. The high incidence of Q_1 in right branch block is mainly due to the frequency of

this deflection in electrocardiograms of this type. When the heart is in a relatively horizontal position, as is usually the case when the patient has left axis deviation or bundle branch block, Q_1 is almost always of left ventricular origin, and its presence or absence is determined by the character of the potential variations at the surface of the left ventricle at the beginning of the QRS interval. In left branch block, it is rare because the potential of the left ventricular surface, and consequently of the left arm, is initially positive. In left axis deviation, it is present when these regions are initially negative and absent when they are initially positive. Since right bundle branch block does not materially affect the potential at the surface of the left ventricle early in the QRS interval, Q_1 persists, unchanged in form, or remains absent, as the case may be, when right branch block develops (Table II).

The rarity of Q_1 in right axis deviation cannot be explained in an entirely satisfactory manner at the present time. In normal persons who display this electrocardiographic peculiarity, the heart is usually in a vertical position. For this reason, initial negativity of the left ventricular surface is transmitted to the left leg, and produces Q deflections in Leads II and III instead of in Lead I. The potential of the left arm resembles that of the right ventricular surface, which is initially positive. In right ventricular hypertrophy the situation is different; the enlarged heart is ordinarily transversely placed. Usually, unlike right bundle branch block, right ventricular hypertrophy has a profound effect upon the potential at the surface of the left ventricle at the very beginning of the QRS interval. This condition is represented in the precordial electrocardiogram by tall R waves, often preceded by Q waves in leads from the right side of the precordium and by small R waves, followed by deep S waves, in leads from the left side of the precordium.[74] In right ventricular hypertrophy, therefore, Q deflections are of right ventricular origin, and depend upon the occurrence of initial negativity at the surface of the right ventricle. Since this initial negativity, when it occurs, is transmitted to the left leg and not to the left arm, which undergoes potential variations like those at the left ventricular surface, Q deflections, when present, appear in Leads II and III and not in Lead I. The data available at the present time afford no satisfactory explanation of the tendency for right ventricular hypertrophy to abolish initial negativity at the left ventricular surface or to induce initial negativity at the right ventricular surface. The solution of this problem must, therefore, be left to the future.

SUMMARY

An initial downward, or Q, deflection in Lead I is very uncommon in human left branch block. When this component occurs in an electrocardiogram otherwise characteristic of this conduction defect, a lesion

of the ordinary muscle of the ventricular septum should be suspected, and a full set of precordial leads should be taken.

A Q deflection in Lead I occurs in about one-half of all cases of left axis deviation, regardless of the criteria employed in selecting examples of this electrocardiographic abnormality. Left axis deviation accompanied by inversion of the T waves in Lead I may sometimes be due to incomplete left bundle branch block when Q_1 is absent, but it is almost never due to this cause when this deflection is present.

The incidence of Q_1 in right branch block is similar to its incidence in left axis deviation. In right axis deviation, this deflection is extremely rare.

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AURICULAR INFARCTION

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A URICULAR infarction, as a distinct entity, is rarely reported, and the possibility or probability of such an occurrence is hardly even mentioned in textbooks on heart disease. Most discussions of myocardial infarction describe an anterior and posterior type, and dismiss other involvement with the statement that infarction after occlusion of the smaller branches of the coronary arteries is unusual because of the collateral blood supply.

In 1938, Bean[1] reported a series of 287 cases of myocardial infarction, including two definite auricular infarcts and one case of syphilitic infarction of the left ventricle in which there was a small scar in the auricular appendage. At that time, he stated: "It is improbable that the rarity of reported cases of infarct of the auricle is a true indication of its incidence." Also in 1938, Feil, Cushing, and Hardesty[2] reported two instances of auricular infarction in thirty-four cases of myocardial infarction. Langendorf,[3] in 1939, reported a case of infarction of the right auricle, with electrocardiographic changes on the day previous to death which were attributed to the lesion. A comparatively larger number of cases of rupture of the heart have been reported, with not infrequent involvement of the auricle, chiefly the right. Infarction of the auricle is regarded as a common cause of rupture. Recently (1942), Cushing, Feil, Stanton, and Wartman,[4] of Western Reserve University, reported 182 cases of myocardial infarction, including thirty-one, or 17 per cent, in which the auricle was involved. This is the highest incidence reported. However, in only six of these was the auricle alone involved, without infarction of the ventricle.

Most experimental evidence and some of the clinical reports suggest that certain electrocardiographic changes may be indicative of the occurrence of auricular infarction, although these are not constant. Disturbances of the auricular mechanism, such as auricular fibrillation, auricular premature beats, auricular flutter, and wandering pacemaker, are considered by some to be the most reliable evidence. Other reports describe an elevation of the P-Ta segment in Lead I with involvement of the left auricle, and similar changes in the P-Ta segments of Leads II and III with lesions of the right auricle. The P waves may be broadened, inverted, diminished or increased in amplitude, slurred, or notched.

Abramson, Fenichel, and Shookhoff[5] were able to produce constant changes in the electrocardiograms of dogs and cats by cauterization of the auricles. When the anterior or posterior surface of the right auricle was injured, the P-Ta segment of Lead I showed a depression, where-

as similar damage to the left auricle resulted in an elevation of this segment. The P-Ta segments of Leads II and III were depressed with cauterization of either right or left auricle, and therefore did not aid in localizing the lesion. Of their observations, these investigators said: "The constancy with which P-Ta segment changes in the dog and cat followed the production of auricular damage leads one to believe that possibly close examination of the comparable portion of the human electrocardiogram might be of value in those instances in which the rare clinical condition of auricular infarction with rupture is suspected."

Although auricular infarction with rupture may be rare, auricular infarction without rupture is apparently a more common occurrence than was formerly supposed, and it is not unreasonable to expect that similar electrocardiographic changes might occur with infarction which did not result in rupture. The observation has been made that these changes may be obscured in some instances by the beginning of ventricular activity (QRS).

Depression or elevation of the P-Ta segments may occur in normal electrocardiograms. However, in a series of 200 normal electrocardiograms[6] in which depression of this segment occurred in Lead I in 55 per cent, it did not exceed 0.8 mm. in any case. Only two records showed an elevation of P-Ta, and in neither of these was it more than 0.4 mm. In another series of 100 normals,[7] elevation of the P-Ta segment was found only twelve times in Lead III and not at all in Leads I or II. Depression was more common; it occurred fourteen times in Lead I, fifty-four times in Lead II, and twenty-one times in Lead III. The maximum deviation in either direction was 0.5 mm. It seems highly probable, therefore, that any electrocardiogram in which the P-Ta segment is depressed (deviates from the normal level) more than 0.8 mm. or elevated more than 0.5 mm. may be considered strongly suggestive of auricular damage, particularly if the changes occur in Lead I.

Because of the dearth of reports of auricular infarction, and also because of the lack of definite diagnostic clinical signs, it was thought of value to report the following cases.* Three of these patients had true auricular infarcts, and the fourth was thought to have auricular infarction because of suggestive electrocardiographic changes, and is included for that reason.

REPORT OF CASES

The first case was that of a man, 36 years of age, who complained of several attacks of substernal pain (under the lower half of the sternum), radiating outward and downward and into both arms below the elbows. Physical examination was entirely negative on two occasions, and an attempt to reproduce the pain by extreme exertion was unsuccessful. An electrocardiogram, taken four months after the first attack, did not show any suggestive variations from the normal. Five days after the electrocardiogram was taken, the patient apparently had an attack of severe pain, associated with vomiting, and died in about thirty minutes.

*These cases were observed in the past year and a half at the Presbyterian Hospital of Pittsburgh.

Autopsy revealed a dark-red, sharply circumscribed, hemorrhagic lesion of the wall of the right auricle (Fig. 1). This area was roughly circular, and measured approximately 1 cm. in diameter. Incision into this area showed that it was a true infarct; the wall at this point was a very dark red as a result of intramural hemorrhage. This lesion was located at, or very near, the auriculoventricular node, just below the opening of the inferior vena cava and to the right of the opening of the coronary sinus. There were no old scars or other lesions. The coronary arteries and their branches showed irregularly distributed sclerosis, and, in some places, were quite hard and almost occluded. This was especially marked in the main vessels.

Fig. 1.

The second case was that of a woman, 58 years old, who was admitted to the hospital with a history of sudden onset of severe dyspnea, with little or no pain. Signs of circulatory failure were evident in the poor quality of the heart sounds, rapid pulse rate, marked cyanosis, moist râles at the bases of both lungs, and slight peripheral edema. The diagnosis on admission was coronary occlusion. An electrocardiogram (Fig. 2), taken the following day, showed inversion of the P waves in Leads II and III, depression of the P-Ta segments in Lead I, and elevation of the corresponding portions in Leads II and III. There was a peculiar, dome-shaped appearance of the P-Q segments in Lead III which might be considered the equivalent of the RS-T changes which are characteristic of ventricular lesions. Because of these changes, involvement of the auricle, presumably the right, by infarction was suggested. The patient died forty-four hours after admission, and autopsy revealed dilatation of the right auricle and a rim of dark discoloration along the A-V junction, extending into the auricular appendage (Fig. 3). On cut section the wall here was infiltrated with blood. There was moderate atheroma of the aorta and coronary vessels, but no occlusion of the large branches. The auricular lesion was reported as due to occlusion of a small vessel in the infarcted area. The right ventricle, left auricle, and left ventricle showed no areas of infarction.

In February, 1943, a woman, 26 years of age, was admitted to the hospital with a provisional diagnosis of congestive failure probably due to rheumatic heart disease, although definite evidence of a valvular lesion

was not present.   Profuse sweating, marked pallor, and moderate
dyspnea were present.   Examination of the heart showed that it was
enlarged to the left; the heart action was irregular, and apparently there
were long periods of coupling. The sounds were accentuated at the apex,
and, at times, a low, rumbling sound suggestive of a murmur was heard
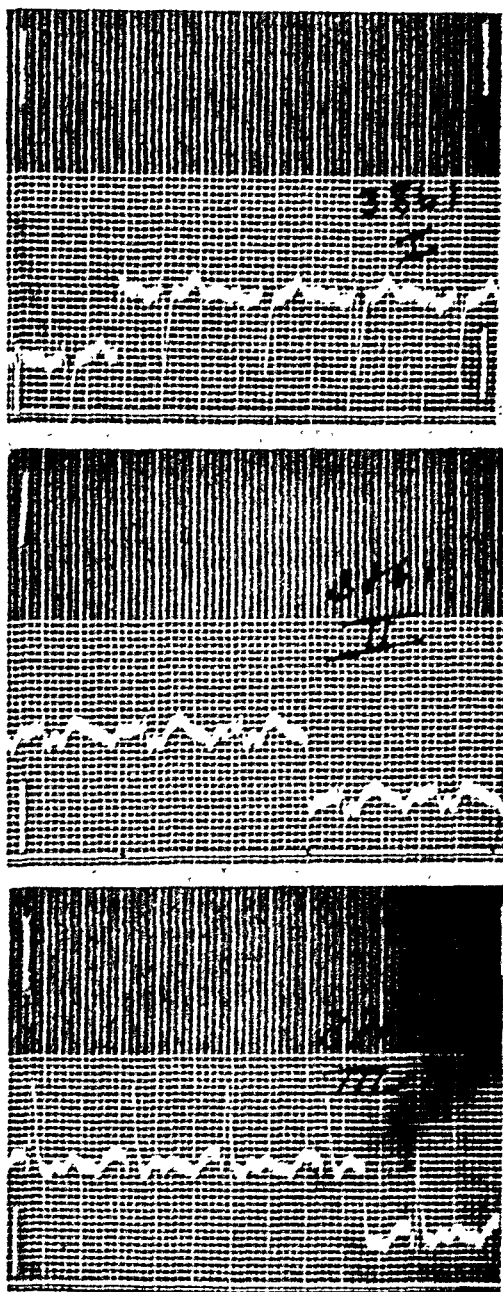

Fig. 2.—See text.

just at the beginning of diastole. A teleoroentgenogram showed extreme
enlargement of the heart with contours suggestive of mitral stenosis. An
electrocardiogram (Fig. 4), taken the day after admission, revealed what
was apparently 2:1 A-V heart block; alternate P waves were fused with
T waves. The P waves were slightly notched in Lead I and peaked in

Leads II and III. Because of large, broad complexes in the usual position of the T waves, it was difficult to ascertain exact deviations from the base line. The P-Ta segments of Leads II and III seemed to be slightly depressed. No adequate explanation could be offered for the unusual changes, but the possibility of coronary thrombosis with unusual effects on the myocardium and conductive mechanism was suggested. Three days after admission, the patient died, and examination of the heart post mortem showed an infarct, about 2 by 3 cm., in the wall of the right auricular appendage. The right auricle was markedly dilated. A large ulceration was found on the interventricular septum below the tricuspid valve, extending through the wall into an aneurysmal sac. Section through the auricular area showed a true infarct. The final diagnosis was acute ulcerative endocarditis and infarction of the right auricular appendage.

Fig. 3.

A white man, 59 years of age, was admitted to the hospital April 5, 1943, with the complaint of severe pain in the jaw, neck, chest, and abdomen which began suddenly while doing light work. The pain was constant, not relieved by rest, and there had been no previous attacks. Physical examination revealed slight pallor, a cold, clammy skin, dyspnea, and moderate cyanosis. There was a systolic murmur at the apex, and also a sound which was interpreted as a pericardial friction rub. The heart rate was 72 per minute, and the blood pressure, 178/110. A tentative diagnosis of coronary occlusion was made, and electrocardiograms (Fig. 5) seemed to confirm this diagnosis. Changes considered suggestive of auricular damage were present, as shown by the broadened, dome-shaped P waves in Lead I, notched, W-type P waves in Leads II and III, and the depressed P-Ta segments of Lead III. These abnormalities were fairly constant in all the tracings taken, but there were some variations, suggesting repair of the lesion, eight days after the onset. Because of the failure of the blood pressure to fall after the initial attack, and also because the pain, as described, was not typically that of coronary occlusion, the diagnosis was considered as only tentative. The pain continued in moderate severity until April 24, when death
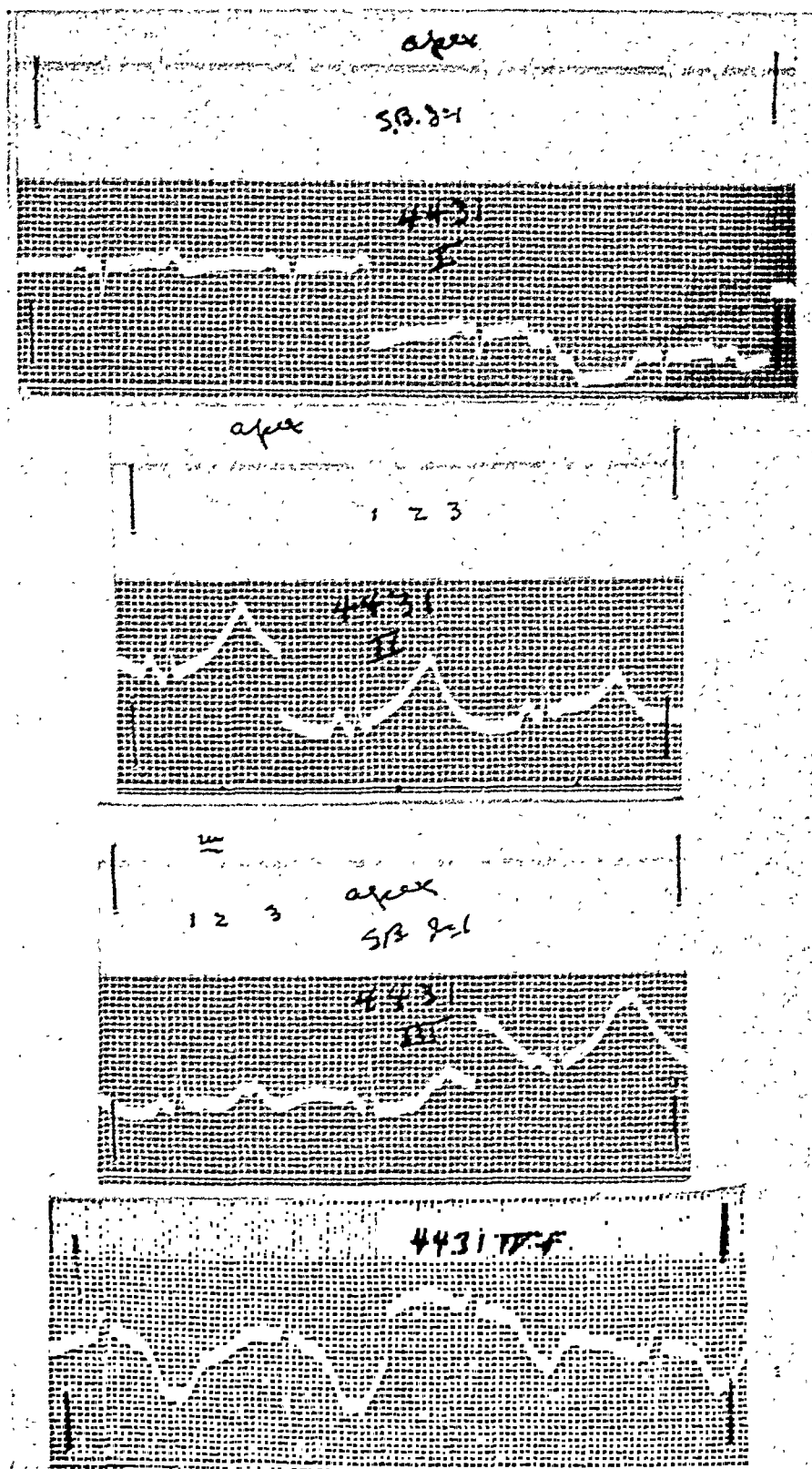
Fig. 4.—Right axis deviation. Large, broad complexes in Leads II, III, and IVF in position of T waves. Sound: variable third heart sound. Vibrations of faint systolic murmur.
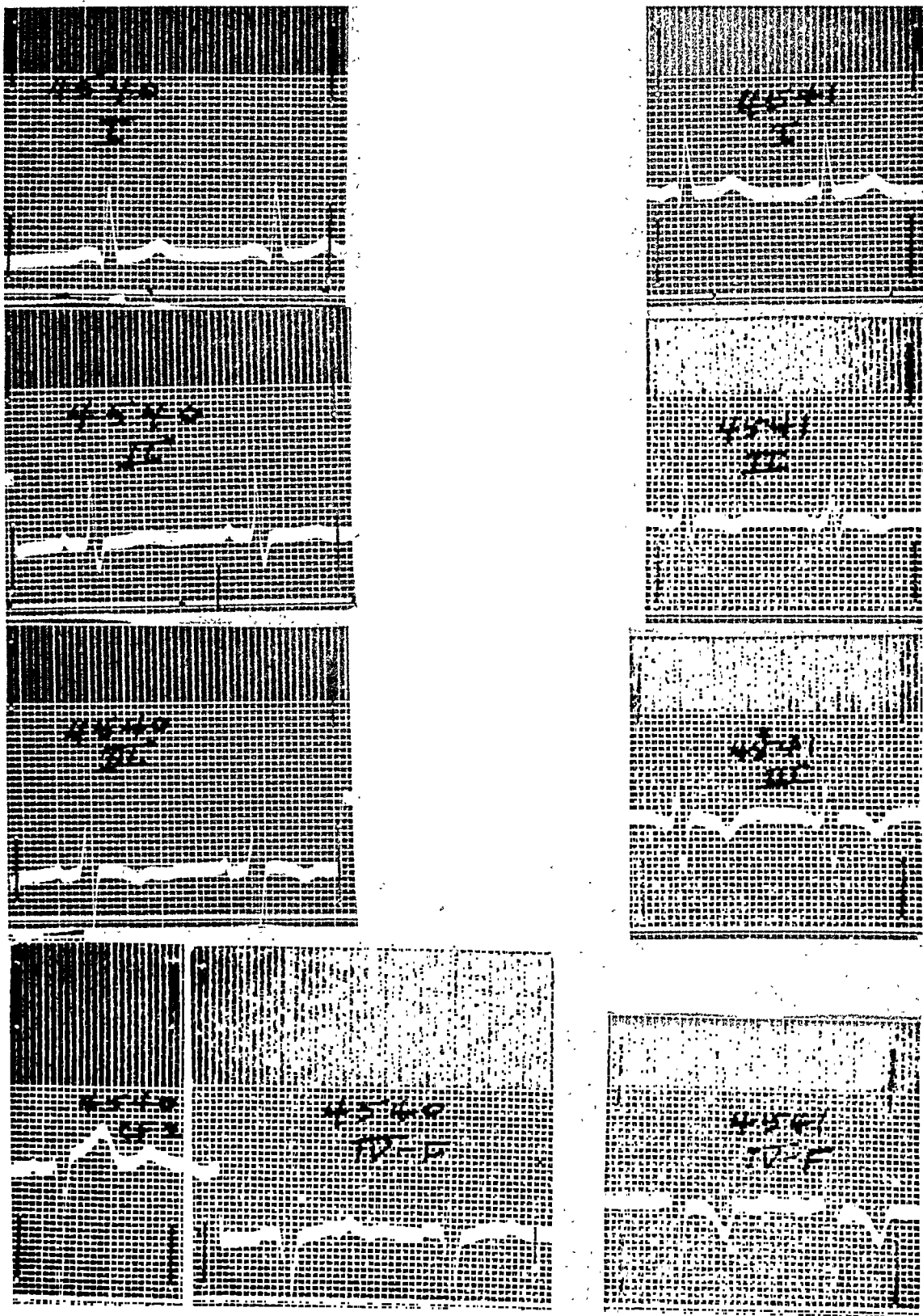
Fig. 5.—April 5, 1943. five and one-half hours after acute pain in left side of jaw, neck, and precordium. P waves flattened in Leads I and IVF. Ventricular complexes show well-developed left axis deviation and moderate slurring. Small Q waves in Leads I, IVF, and CF₅: T waves up in Lead I, diphasic in Lead II, inverted in Lead III, up in Leads CF₂ and CF₅, and diphasic in Leads CF₃ and IVF.

April 6, 1943, twenty-seven and one-half hours after attack. P smaller in Lead I, split in Leads II and III. P-Ta depressed in Lead III. T waves negative in all leads.

occurred suddenly. On post-mortem examination of the chest, the left pleural space was found to be filled with blood and clots, compressing the left lung upward so that it occupied only one-fifth of its usual space. The pericardium was adherent to the lateral chest wall, but the cavity was dry when opened. The heart, aorta, and mediastinal structures were removed en masse, and the source of the bleeding was found to be rupture of a false aneurysmal sac at the level of the fifth thoracic vertebra. At the level of the origin of the left subclavian artery, there was a tear in the aorta at a thinned-out area, at which point the surrounding connective tissue was thickened and adherent. Distally along the course of the aortic arch and the beginning of the descending aorta, thickened mediastinal pleura formed a false aneurysm which was partially filled with thrombus, the rupture of which had produced the fatal hemorrhage. Sclerotic patches were present on the intima, and interstitial hemorrhage extended proximally along the arch and *involved the auricles*, particularly the right. The left ventricle was thickened and somewhat dilated. The auricles were dilated. There were small calcified areas on the valve cusps, and an old, healed vegetation was seen on one cusp of the mitral valve. The coronary openings were patent, and the coronary arteries were sclerotic and tortuous, but no evidence of myocardial infarction was seen. No auricular infarct was found in this case; however, the hemorrhage into the auricles may have produced sufficient damage to cause the changes noted in the P-Ta segments of this patient's tracings.

SUMMARY

Three cases of distinct auricular infarction, without ventricular involvement, are presented. A fourth case in which the electrocardiograms showed changes apparently typical of auricular damage proved to be one of ruptured, false aneurysm, with hemorrhagic infiltration of the auricles.

The first case was interesting because of the unfortunate location of the small infarct; it might have been less serious if it had been located in the ventricle.

In three of the four cases there were deviations of the P-Ta segments conforming to that described as typical of auricular damage. In one there was also an apparent disturbance of the A-V conduction pathway; this was most likely due to the ulceration through the interventricular wall.

All of the infarcts were located in the right auricle.

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THE EFFECT OF CHRONIC LEAD POISONING ON ARTERIAL BLOOD PRESSURE IN RATS

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RECENTLY, Fouts and Page[1] reported their inability to produce arterial hypertension in one dog which was chronically poisoned with lead over a period of three years. A second dog, poisoned for a much shorter time, likewise failed to develop hypertension. They state that "the belief that chronic lead poisoning leads to arterial hypertension extends deep into the annals of clinical medicine, but the evidence on which it is based is unconvincing," and conclude from their negative results that "the problem in human beings needs reinvestigation."

Although conclusions from studies on animals cannot always be carried over to man, it would certainly seem that lead would be an unlikely cause of hypertension in man if it could not produce hypertension in an animal, especially in an animal which is known to be capable of developing hypertension from some other cause. Therefore, it seemed well to repeat the study with a different species of animal.

METHOD

Healthy albino rats, weighing 150 to 200 grams, were used. Fifteen were successfully carried through the experimental procedure. Lead acetate was given in a dose of 90 mg. daily, omitting every seventh day throughout the experimental period. This corresponds to about 70 mg. of lead, as such, per day, and was given dissolved in 2 c.c. of water by stomach tube.

The blood pressure was measured by the indirect method described by Griffith,[2] and, in two animals, directly by inserting a needle into the abdominal aorta. This needle was connected by a rubber tube, filled with saline, to a mercury manometer, the inertia of which was so great that there was no visible pulsation in the mercury column. Under such circumstances, the pressure measured is mean pressure, in contrast with the indirect method, which is thought to measure systolic pressure. Hereafter, the term "blood pressure," when unqualified, will indicate blood pressure measured by the indirect method.

In ten of the fifteen animals, the blood pressure was measured before beginning the administration of lead, and found to be normal. In the remaining five animals, the blood pressure was first measured ten days after beginning the administration of lead, and found to be normal at that time. It was therefore assumed that it had been normal initially. Thereafter, the blood pressure was measured every fifteen to twenty days, depending upon convenience. More frequent readings were considered impractical because each necessitated induction of surgical anesthesia with ether. The blood pressure was measured four times in four

animals, three times in seven animals, and twice in three animals. All
animals charted survived at least until the thirtieth day, after which,
some were sacrificed for acute experiments and some died; four animals
survived until the experiment was terminated on the eightieth day.
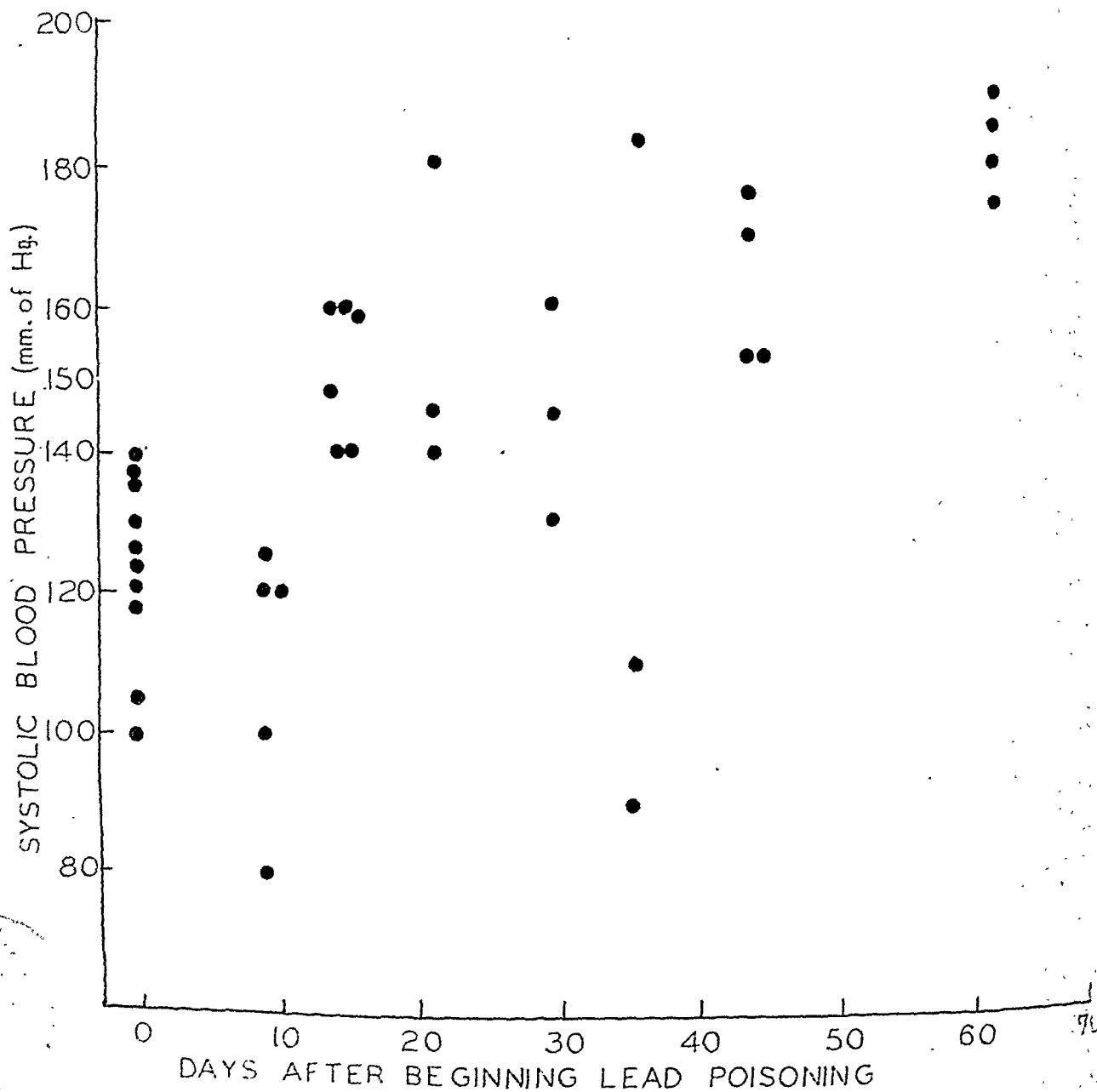
Fig. 1.—Chart showing the effect of chronic lead poisoning on the systolic blood
pressure of fifteen rats.

RESULTS

The results are shown in Fig. 1, in which only the indirect measure-
ments are charted. The horizontal line at 150 mm. represents the upper
limit of normal by this method. It is apparent that all animals that
survived forty days were hypertensive.

The mean blood pressure, measured directly by a needle in the aorta, normally does not exceed 90 mm. of mercury.   In two hypertensive animals in which the blood pressure was measured by both methods, the results were as follows:

Rat 1.—Indirect (systolic) blood pressure, 180 mm. of mercury; direct (mean) blood pressure, 119 mm. of mercury.

Rat 2.—Indirect (systolic) blood pressure, 160 mm. of mercury; direct (mean) blood pressure, 122 mm. of mercury.

CONCLUSION

Chronic lead poisoning can produce arterial hypertension in rats.

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AN ELECTROCARDIOGRAPHIC AND CLINICAL STUDY OF VARIOUS SO-CALLED CARDIAC DRUGS

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FOR years, many pure glycosides have been in common use in the treatment of congestive heart failure. Many of these have been given parenterally in the hope of facilitating rapid digitalis action.[1] Until recently, there has been little in the literature to prove that they act rapidly, and their use in the past has been based entirely on the claims of their various manufacturers. In a previous communication, one of us[2] observed the rapid effect of one of these glycosides on the electrocardiograms of two normal control subjects at ten-minute intervals for a period of two hours or more, and subsequently noted the effect of this glycoside at frequent intervals in many cases of congestive heart failure. The electrocardiographic changes appeared to follow a characteristic form in all subjects under observation. This led us to believe that some electrocardiographic change might typify each of the various glycosides, and that these changes might be characteristic of specific drug action on the myocardium. Since this initial observation, we have noted varying electrocardiographic changes after the use of many glycosides, and we believe that this warrants further study.

The effects of various digitalis bodies on the electrocardiogram of man and animal have been recorded frequently.[3-6] Most of these studies were mainly concerned with general changes in the polarity of the T wave. No attempt was made to evaluate the changes in the RS-T segment and T wave quantitatively and individually for each preparation used. Other studies failed to record characteristic digitalis effect because of failure to evaluate the action of the drug in the various electrocardiographic leads. McMillan and Bellet[7] called attention to various changes in the S-T segment and other electrocardiographic components after the administration of digitalis which they felt were quite characteristic. Our observations lead us to believe that, if all of the above factors be taken into consideration, the electrocardiographic criteria of a digitalis effect are quite dependable. Furthermore, we have been led to believe that many digitalis glycosides[8] vary in their effect on the electrocardiogram.

Changes in the RS-T segment and T waves are not entirely limited to the action of digitalis. It is generally accepted that many physiologic and pathologic changes in the myocardium alter these constitu-

ents. Coronary anoxemia,[9] hyperventilation,[10] and innumerable changes in cardiac function are known to produce both segment changes and alteration in the polarity of the T waves. Master, Friedman, and Dack[11] have shown that, after exercise, a general depression of the RS-T segment and T waves may occur in the presence of coronary insufficiency. This study suggests that digitalis depression of these electrocardiographic components may be the result of cardiac anoxia. Digitalis effects on the electrocardiographic constituents have been variously described by Oettel,[12] Gold and his co-workers,[13] and others.[14-18] Wegria and his associates,[19] in a recent study, felt that changes in the electrocardiogram after digitalis administration appeared to be characteristic for each type of preparation used.

The use of the electrocardiogram for clinical standardization of digitalis preparations has been suggested by many clinicians. These observations have been discounted in the past, and we are led to believe that a more detailed study, embracing all phases of electrocardiographic change caused by various digitalis preparations, may lead to a more consistent series of observations. Although our observations are preliminary, we feel that they support this contention.

TABLE I

DRUG USED	DOSAGE ADMINISTERED	METHOD OF ADMINISTRATION
Digifolin (Ciba)	4 c.c., 2 cat units	Intravenously
Digalen (Roche)	4 c.c., 2 cat units	Intravenously
Digilanid (Sandoz)	8 c.c., 4.8 cat units	Intravenously
Ouabain (Smith)	4 c.c., 10 cat units	Intravenously
Cedilanid (Sandoz)	8 c.c., 1.6 mg.	Intravenously
Digoxin (B. W. & Co.)	3 c.c., 3 cat units	Intravenously
Scillaren-B (Sandoz)	1 c.c., 1 cat unit	Intravenously
Strophosid (Sandoz)	2 c.c., 1 mg.	Intravenously
Strophanthin-K (Abbott)	2 c.c., 0.5 mg.	Intravenously
Coramine (Ciba)	1.5 c.c. (Pyridine beta-carboxylic acid diethyl-amide of nicotinic acid)	Intravenously
Metrazol (Schering)	1 c.c. (1½ grains of penta-methylenetetrazol)	Subcutaneously

The drugs listed in Table I were given in the dosage recommended by the manufacturer. All preparations, with the exception of metrazol, were given rapidly by the intravenous method. In the case of digoxin, the recommended dose was diluted with physiologic saline to make a total volume of 10 c.c.

METHOD OF STUDY

Each preparation was given to two subjects who were free from cardiovascular disease. Normal renal function was a prerequisite in each case. Investigation was made to ascertain whether or not the subjects had drug idiosyncrasies. Prior to the study, an electrocardiogram was recorded in the four conventional leads recommended by the American Heart Association. A Sanborn Cardiette and a portable Cambridge machine were used alternately, and were so standardized that a 1 cm. deflection represented a potential difference of 1 mv. Each subject was

placed in a supine position, where he remained until the completion of
the study. After the administration of each drug, Lead II was recorded
at ten-minute intervals for a period of not less than two hours. When
no electrocardiographic change was noted after one hour's observation,
the study was discontinued. Throughout the period of observation, each
subject was examined from time to time, and interrogated relative to the
appearance of untoward symptoms.

RESULTS OF STUDY

1. *Cedilanid (Lanatoside C).*—The average heart rate of the two
subjects that received 1.6 mg. of Lanatoside C was 90 per minute at the
commencement of the experiment. An appreciable reduction of this rate
was not noted until two hours after the administration of the drug, and
this reduction was only 5 beats per minute. One subject had frequent
ventricular ectopic beats before the drugs was given, and these dis-
appeared completely throughout the period of observation. In both
subjects, a gradual depression of the RS-T segment was noted, begin-
ning 10 minutes after the drug was administered and continuing for
a period of from 90 to 100 minutes. At this time, the RS-T depression
reached its maximum of 2 mm. A return of this depression was first
noted 110 minutes after the drug was given, and a gradual return of
this segment to normal occurred in approximately twenty-four hours.
The positive polarity of the T waves in both subjects diminished, and
could be considered isoelectric 80 minutes after the drug was given.
The T waves remained in this isoelectric state throughout the entire
period of observation, and, at the end of twenty-four hours, their for-
mer positive polarity was still mainly lacking. Neither subject pre-
sented untoward symptoms or physical signs attributable to Lanatoside C.

2. *Ouabain.*—One subject received 10 cat units of ouabain which was
recommended as active, although its potency expiration date had almost
arrived. This preparation was found to be ineffective, clinically and
electrocardiographically. The remaining subject received fresh ouabain
solution directly from the manufacturer. The effect of the drug was
almost immediate on both the heart rate and the electrocardiogram. At
the end of 130 minutes of observation, the heart rate was reduced from
92 per minute to 52 per minute. This marked sinus effect continued for
four hours after the completion of the experiment. The maximum de-
pression of the RS-T segment was noted ten minutes after the drug was
given. The T wave also showed its maximum depression within ten min-
utes. The quantitative depression of the RS-T segment and the T wave
approximated more than 1 mm. at this time. Both of these components
gradually increased their positive polarity, and, at the end of 120 min-
utes, two-thirds of their depression had been nullified. This rapidity of
action on the electrocardiogram was unlike any of the other glycosides
used in this study. It possibly accounts for the sudden deaths which we
have observed when it has been given to patients with congestive heart
failure who had been receiving digitalis previous to its administration
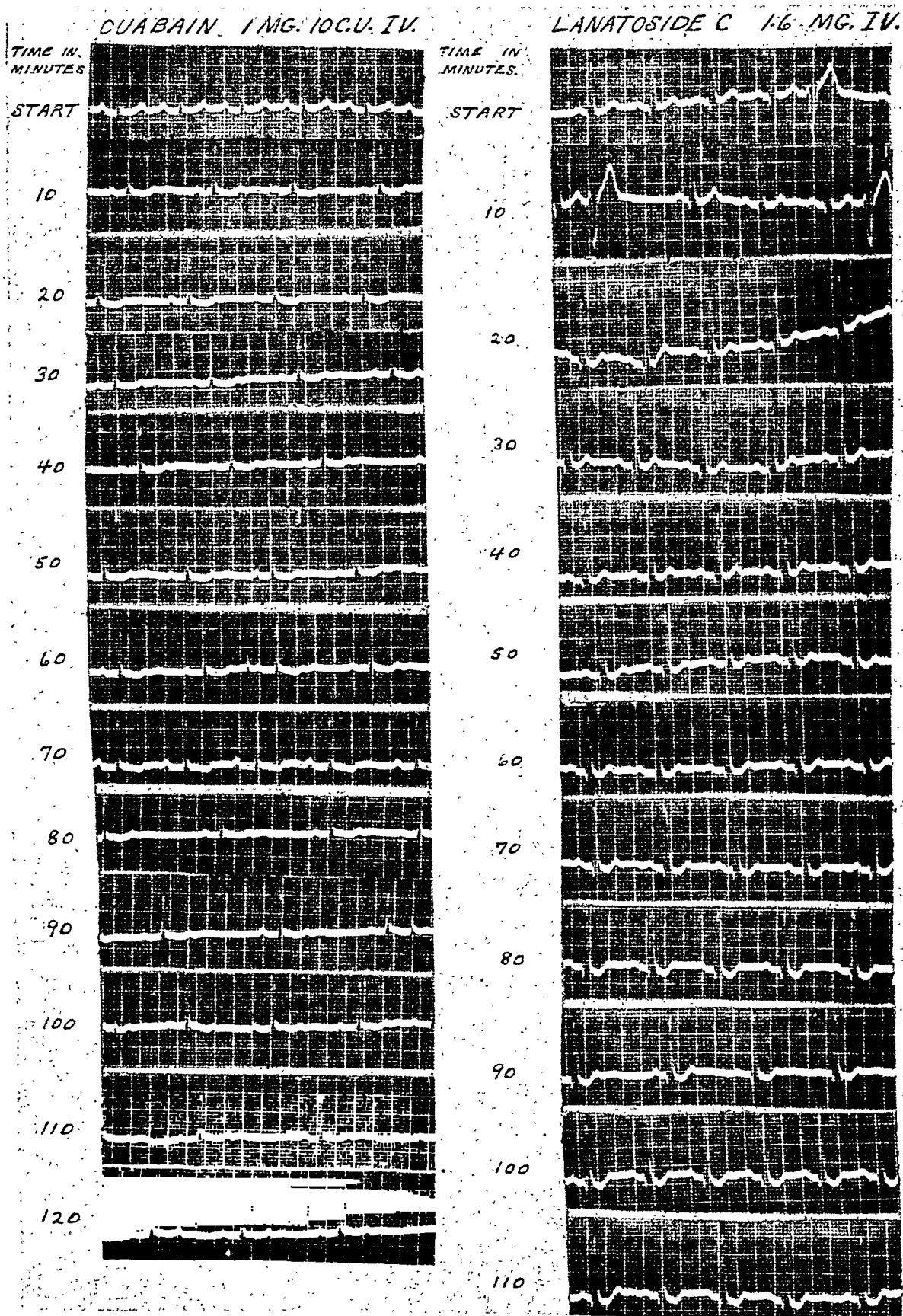
Fig. 1.—Comparative serial electrocardiograms recorded in Lead II. (Note rapid change with ouabain and gradual change with Lanatoside C on RS-T segment and T wave.)
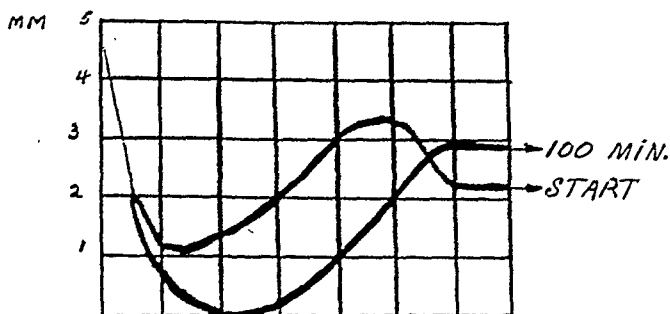
CEDILANID-(SANDOZ)- 1·6 MG.

Fig. 2.—Maximum cedilanid deflection. 1 cm. ≅ 1 mm. on electrocardiogram.
Diagrammatic Scheme.—Changes in the electrocardiographic pattern of the RS-T segment and T wave before and after* the intravenous† administration of the various cardiac glycosides.

Scale 1 cm. equals 1 mm. on actual tracings.

*In the case of ouabain, a return of the pattern to normal is noted.
†Metrazol was given subcutaneously.
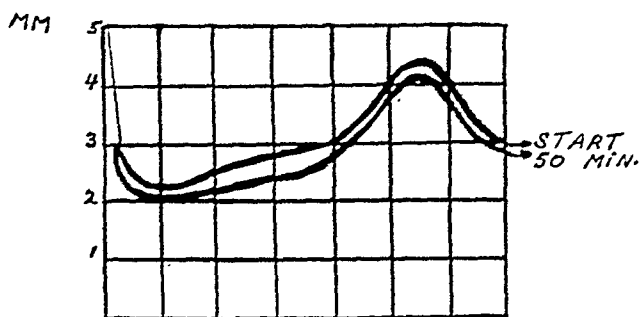
OLD OUABAIN-(SMITH)-10 C.U.

Fig. 3.—Inert ouabain (old). Maximum effect. 1 cm. = 1 mm. on the electrocardiogram.
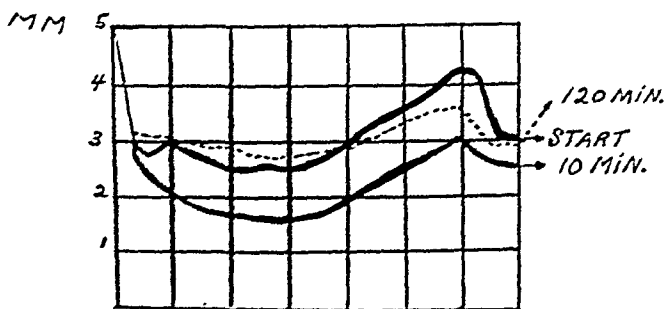
FRESH OUABAIN-(SMITH)-10CU.

Fig. 4.—Fresh ouabain. Maximum deflection in ten minutes. Dotted line represents return to normal in two hours.
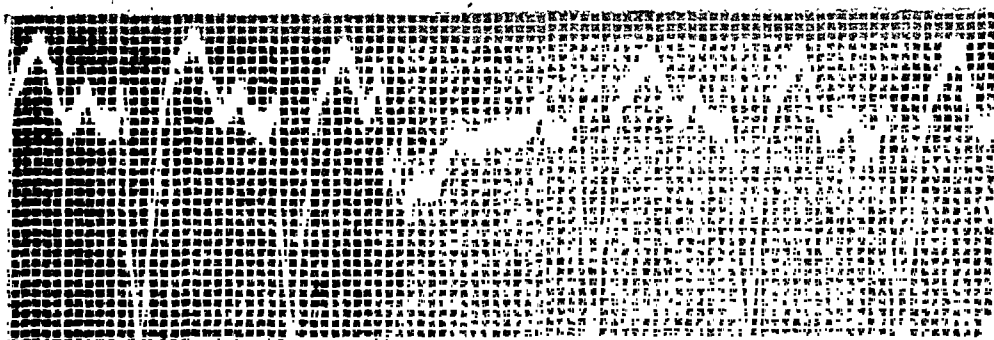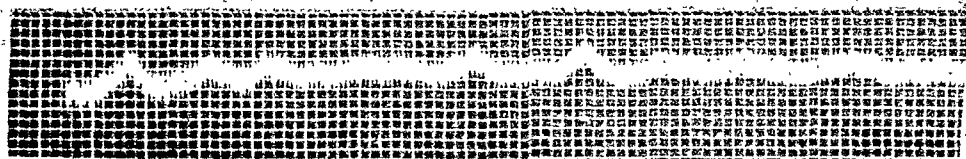
Fig. 5.—F. H., female, age 68 years. Admitted Apr. 12, 1943, with diagnosis of hypertensive heart disease and congestive failure. Electrocardiogram recorded in Lead III demonstrates bundle branch block and ventricular premature contractions. *A*, Ouabain was given intravenously, prior to history of maintenance digitalis therapy. *B*, Within sixty seconds ventricular fibrillation and death resulted.
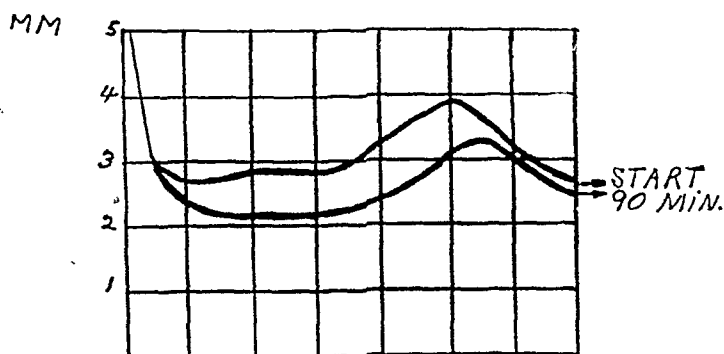
DIGOXIN-(B.W.&CO.)- 3 C.U.

1.

Fig. 6.—Maximum digoxin effect. 1 cm. = 1 mm. on the electrocardiogram.
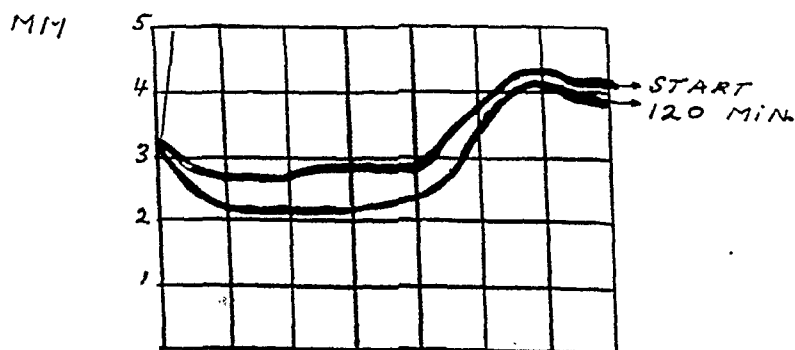
DIGALIN-(ROCHE)- 2 C.U.

Fig. 7.—Digalen. 1 cm. = 1 mm. on the electrocardiogram.

(see accompanying electrocardiogram of F. H.). There was no evidence of an ouabain effect electrocardiographically, eight hours after the drug was administered.

3. *Digoxin.*—After the intravenous administration of 3 cat units of this drug, gradual depression of the RS-T segment was noted in both subjects. This depression reached its maximum in 120 minutes, and measured 3/4 mm. The T wave was gradually depressed in a like manner, and, at the end of 120 minutes, was lowered 1/2 mm. The action of this drug on the electrocardiogram was not unlike cedilanid, but the degree of depression was far less. As in the case of cedilanid, digoxin produced an almost negligible early sinus effect. The maximum reduction in heart rate throughout the entire 120-minute period of observation was six beats per minute. Evidence of digoxin effect was still apparent eight hours after the completion of the study. No untoward symptomatic or physical effects were noted in either subject throughout the entire course of the study.

4. *Digalen.*—Although the RS-T segment and T wave were depressed only 1/2 mm. in each subject, a moderate sinus effect occurred in both throughout the 120-minute period of observation. The average reduction in heart rate was 10 beats per minute. This reduction was first noticed 30 minutes after the drug was administered, and continued throughout the 120-minute period of observation. Eight hours after the study, the sinus reduction no longer obtained, but the 1/2 mm. of RS-T segment and T-wave depression was still apparent. No untoward symptomatic or physical changes attributable to this drug were noted throughout the entire period of study.

5. *Digilanid.*—After the intravenous administration of this drug (4.8 cat units), a gradual reduction in heart rate was noted; this continued for the entire 130 minutes of observation, and averaged 14 beats per minute. A slight sagging effect on the RS-T segment occurred in 20 minutes, and this continued for 70 minutes after the drug was administered, at which time it reached its maximum depression of 1/3 mm. The depression of the T wave occurred gradually after the drug was administered, and, at the end of 130 minutes, the depression reached its maximum of 1 1/2 mm. On a previous study, 2 cat units of this drug were administered to a subject, and the only noticeable effect on the electrocardiogram was a 1/8 mm. depression of the descending limb of the T wave. No untoward symptoms resulted from the administration of this drug.

6. *Strophanthin-K* (Abbott).—One mg. of this drug was given intravenously to two subjects without producing untoward symptoms or physical signs. Throughout the entire experiment, which was conducted for a period of two hours, little or no effect was noted on the RS-T segment and T wave. In one subject there was a slight, questionable depression at the commencement of the RS-T segment. The sinus effect on the heart rate was negligible.

7. *Strophosid* (Sandoz).—Each of two subjects received one mg. of this drug intravenously without untoward clinical effects. Changes in the RS-T segment throughout the entire study were negligible. The only effect on the T wave was a ½ mm. depression of its descending limb. No sinus effect was noted.
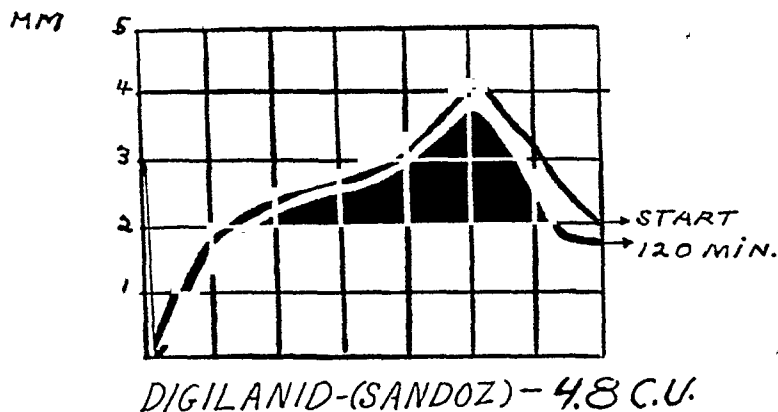
Fig. 8.—Digilanid, maximum deflection. 1 cm. = 1 mm. on the electrocardiogram.
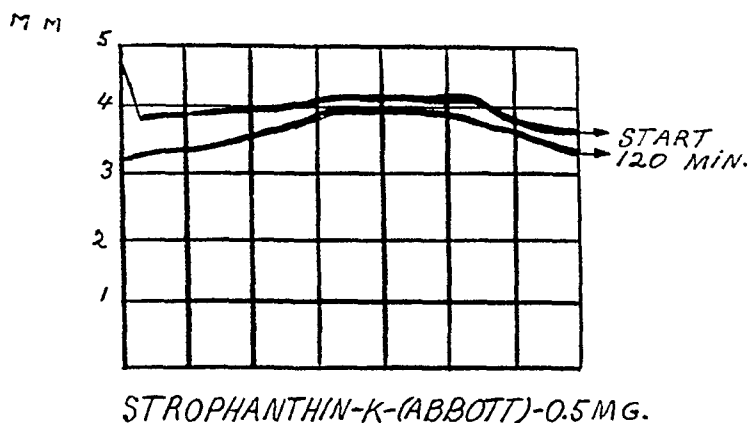
Fig. 9.—Strophanthin-K. Maximum deflection. 1 cm. = 1 mm. on the electrocardiogram.
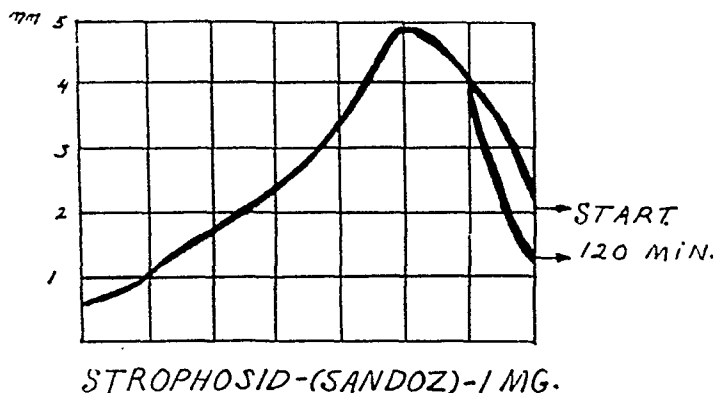
Fig. 10.—Strophosid. Maximum deflection. 1 cm. = 1 mm. on the electrocardiogram.

8. *Scillaren-B.*—Two subjects received 0.144 mg. of this drug without untoward clinical effects. No change in the RS-T segment occurred throughout the entire period of observation. Very slight depression of the descending limb of the T wave was noted 80 minutes after the drug

was given. A slight sinus reduction in heart rate occurred within 10 minutes after the drug was administered, and continued throughout the entire period of observation.

9. *Metrazol.*—This drug was given subcutaneously to two subjects in 2 c.c. doses (3 grains). Approximately 20 minutes after the drug was given, an increase in the depth of respiration was observed. No other clinical change occurred. The RS-T segment, 20 minutes after the drug was given, revealed slight depression (1 mm.), and this depression continued for approximately 60 minutes. This segment change disappeared at thhe end of two hours. Forty minutes after the administration of this drug, a very slight increase in the positive polarity of the T wave was observed (⅓ mm.). This slight increase in positive polarity continued throughout the entire period of observation. An appreciable sinus reduction in the heart rate of approximately 25 beats per minute was noted at the end of two hours.
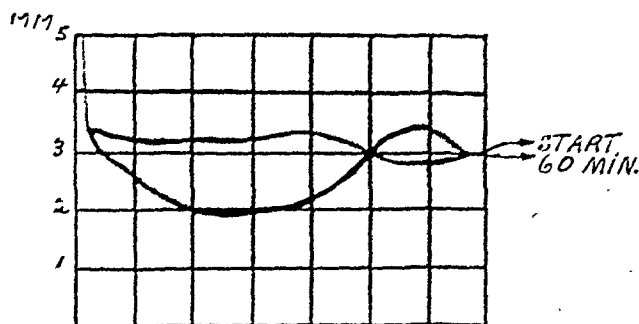
METRAZOL-(SCHERING)-1½ GR.

Fig. 11.—Metrazol (given subcutaneously). Maximum effect of 1½ grains. 1 cm. = 1 mm. on the electrocardiogram.
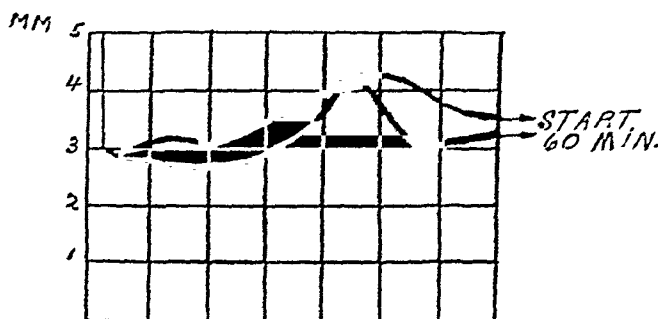
CORAMINE- (CIBA) 1·5 CC.

Fig. 12.—Coramine. Maximum deflection. 1 cm. = 1 mm. on the electrocardiogram.

10. *Coramine.*—Three c.c. of this drug were given to two subjects without noticeable clinical effect. The only electrocardiographic change appeared to be slight shortening of the QT interval. A questionable ¹⁄₁₀ mm. sagging of the RS-T segment was observed in one subject. No sinus effect was noted.

DISCUSSION

Of the various glycosides administered to normal subjects in this study, only three, cedilanid, digoxin, and ouabain, produced significant electrocardiographic change within the two-hour serial study. It is interesting that cedilanid and digoxin act in a similar manner by producing gradual depression of the RS-T segment and T wave, although the former did so more significantly. These drugs are similar in chemical make-up. Digoxin is known to be a degradation product of cedilanid. In the case
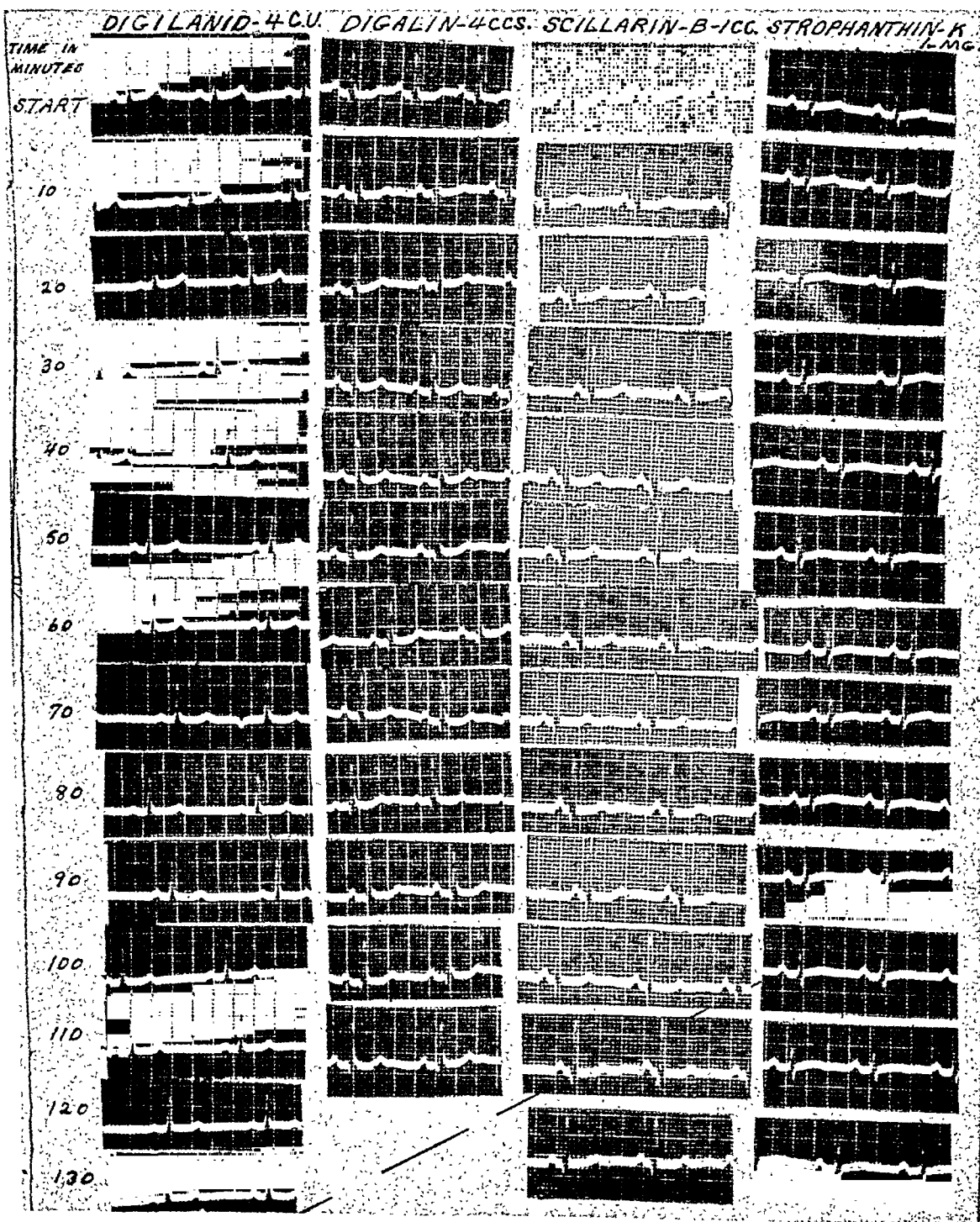
Fig. 13.—Representative serial electrocardiograms, recorded in Lead II following intravenous drugs. (Note sinus effect.)

of active ouabain, the maximum effect on the RS-T segment and T wave occurred within ten minutes after the intravenous administration of the drug. This rapidity of action may in some way be related to the toxic effects occasionally noted when it is given to patients who are already fully digitalized. The return of the electrocardiographic components toward normal seems to follow, inversely, the pattern of electrocardiographic effect. The ouabain effect on the electrocardiogram was two-thirds nullified at the end of the two-hour period of observation, whereas the effects of both cedilanid and digoxin remained almost at a
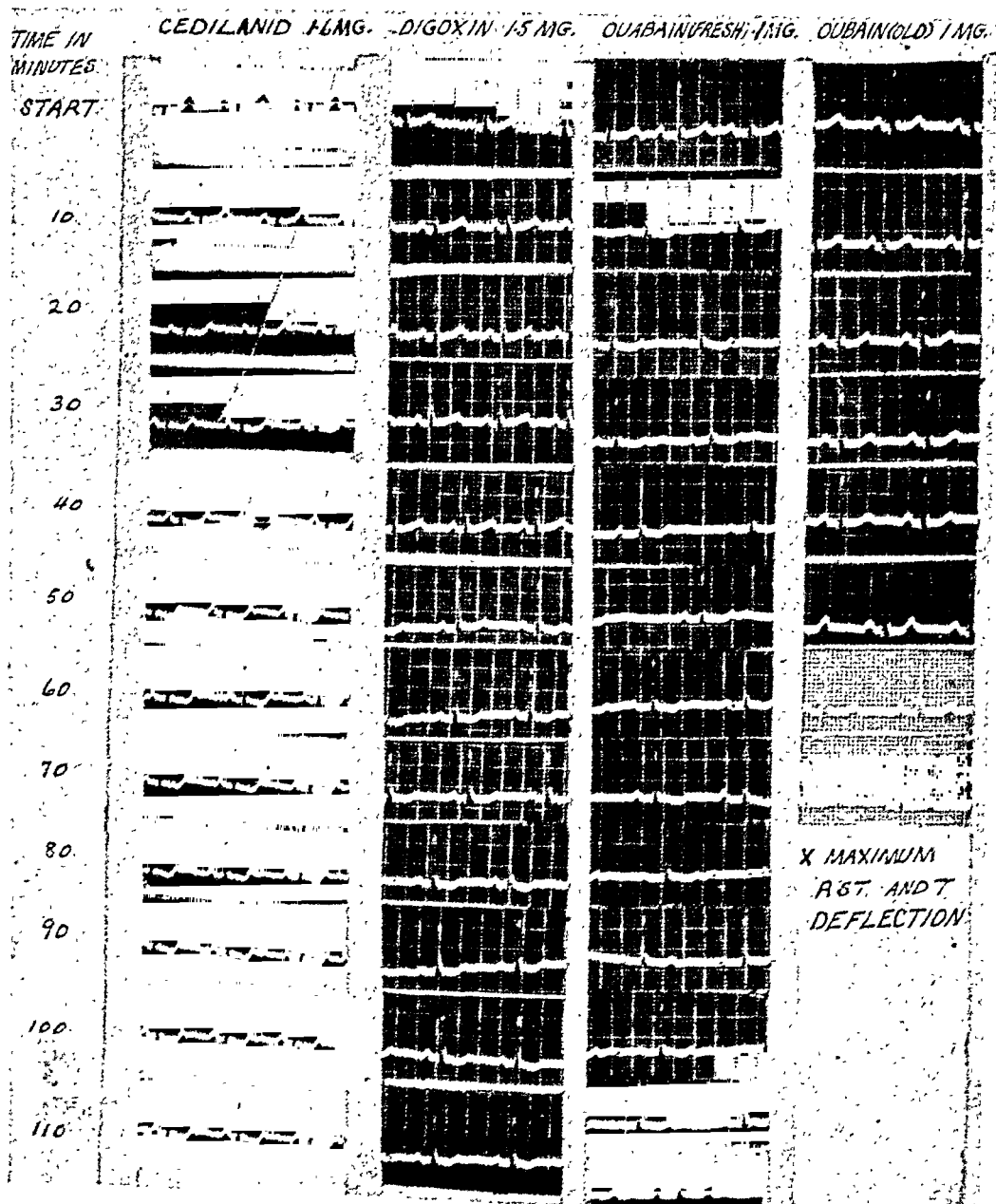
Fig. 14.—Representative serial electrocardiograms using the various glycosides. Recorded in Lead II. Full digitalizing dosage was given intravenously.

maximum until the study was completed. Of these three drugs, ouabain produced the most significant sinus effect. Digalen and digilanid had little electrocardiographic effect. It is quite likely that, had this study been extended, significant changes would have occurred. Both Strophanthus glycosides used in this study failed to produce appreciable electrocardiographic change. The same was true of the glycoside of squill. Metrazol produced slight segment depression which continued for approximately sixty minutes, and, at the completion of our study, a noticeable increase in the positive polarity of the T wave was present. This change we are unable to explain. The effect of coramine was negligible.
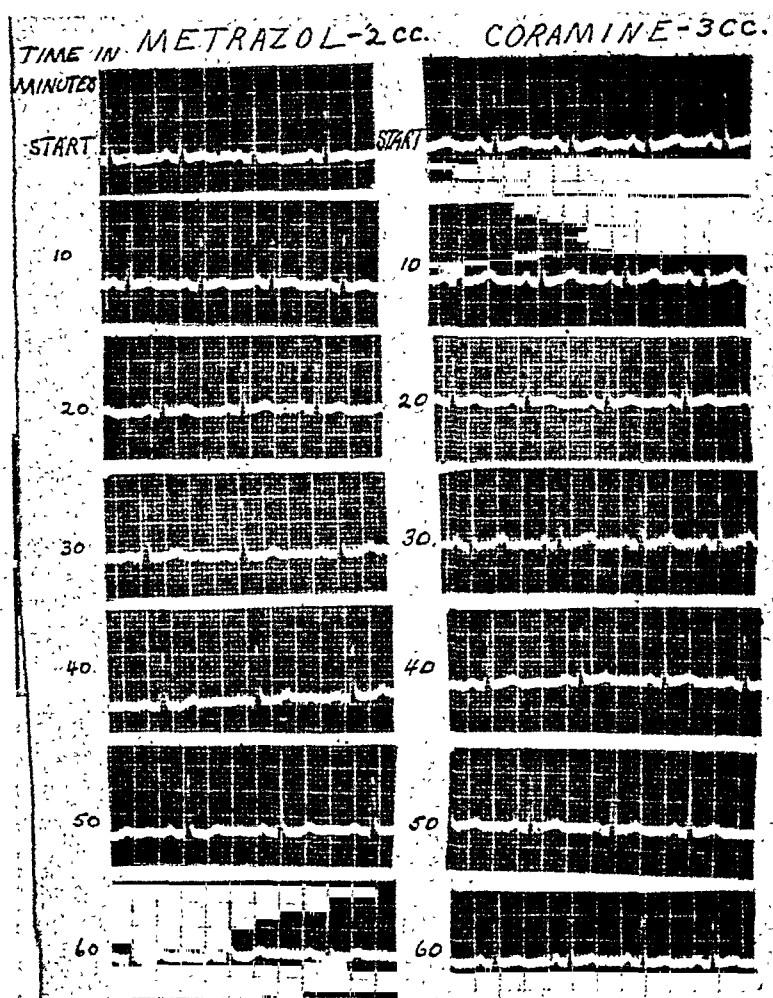
Fig. 15.—Serial electrocardiograms on cardiac glycosides, recorded in Lead II.

The foregoing observations suggest a selective electrocardiographic effect for at least some of the drugs used in this study. The actual significance of these observations is open to further investigation.

SUMMARY

1. Three cardiac glycosides, namely, cedilanid, digoxin and ouabain, produced appreciable and characteristic electrocardiographic changes within the two-hour period of observation.

2. The effects of cedilanid and digoxin were gradual, but the former produced a more significant change, quantitatively.

3. A fresh preparation of ouabain produced significant electrocardiographic change that can be considered maximum for this drug within ten minutes after administration.

4. This ouabain effect was two-thirds nullified at the end of two hours, whereas the effects of cedilanid and digoxin remained almost at their maximum until the study was completed.

5. The foregoing observations suggest that there is a selective action of these drugs on the electrocardiogram, and this selectivity warrants futher study.

6. Metrazol produced an electrocardiographic change which was unlike that produced by the glycosides.

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ON THE MECHANISM OF THE ELECTROCARDIOGRAPHIC SYNDROME OF SHORT P-R INTERVAL WITH PROLONGED QRS COMPLEX

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THE subject of this paper, namely, the electrocardiographic phenomenon of a short P-R interval followed by a prolonged QRS complex, has been heretofore judged to be of academic interest only. Actually, it is part of a syndrome manifested by heart consciousness which occurs in patients who have a tendency to paroxysmal arrhythmias. These ectopic rhythms may have their focal origins in either auricles or ventricles. Although they are often more annoying than dangerous, the fact that there is always a potential hazard was pointed out recently by Wood, Wolferth, and Geckeler,[1] who reported the sudden death of a boy of 13 years.

Knowledge of the mechanism of this peculiar syndrome is still in its hypothetic stage. The hypothesis advanced by Holzmann and Scherf[2] and Wolferth and Wood[3] is essentially as follows:

Some hearts possess, in addition to the normal conduction system, an aberrant pathway connecting one of the auricles with one of the ventricles. Through this aberrant pathway, early stimulation of one of the ventricles may occur. The relatively later spread of excitation to the other ventricle is the cause of the prolongation of the QRS complex.

This hypothesis was recently supported by the experimental evidence of Butterworth and Poindexter.[4] By short-circuiting the normal conduction system through an amplifier, they were able to reproduce the electrocardiographic picture in animals. In a recent communication,[5] clinicolaboratory evidence was presented in favor of this hypothesis. It was suggested that the QRS complex in the syndrome may, in some cases, be the result of simultaneous functional activity of the aberrant and normal pathways. Histologic proof of the existence of accessory conduction connections between the auricles and the ventricles of a patient with this type of electrocardiographic abnormality was recently furnished by Wood, Wolferth, and Geckeler.[1]

If the assumption of an aberrant conduction pathway is correct, it should be possible to modify conduction by means of drugs (or otherwise), either in it or the normal conduction tissue in such a manner as to obtain functional release of one or the other. Depression of the functional activity of the aberrant tissue should divert the electrical

impulse exclusively through the A-V node, and, in so doing, rectify the conduction time relationships in the electrocardiogram. If, on the other hand, the A-V node could be depressed at a time when the electrocardiogram pattern is normal, the aberrant mechanism, being the sole pathway, should give rise to an electrocardiographic pattern consisting of abnormal complexes.

A case suitable for this sort of clinical investigation recently presented itself at Seaview Hospital.

H. W., a 31-year-old colored man, was admitted Feb. 12, 1942. His past history included pneumonia and influenza in childhood and gonorrhea in adolescence. For several years prior to admission, he had had occasional pains in various joints and had noted occasional palpitation on slight exertion. In November, 1941, he developed a cough with a small amount of yellowish sputum, asthenia, and loss of weight. In December, 1941, he was very ill, with elevation of his temperature to 103° F.

On physical examination, a dorsal scoliosis was noted. The lungs were normal clinically and roentgenographically. The heart sounds were of good quality and regular. The rate was 80 per minute. A soft systolic murmur was heard at the apex of the heart. Fluoroscopic examination revealed no abnormalities of the cardiovascular silhouette. The blood pressure was 140/80. There were no evidences of heart failure. The hands and feet were cool. The radial arteries were thickened. The blood cell counts were normal, the blood was normal from the chemical standpoint, and the blood Wassermann reaction was negative. Urinalysis showed a faint trace of albumin and an occasional erythrocyte and leucocyte. The electrocardiogram showed a short P-R interval with prolonged QRS complex (Fig. 1, B). The clinical course was uneventful. Many sputum and gastric examinations for acid-fast bacilli yielded negative results. The blood pressure was variable, and, at times, reached hypertensive levels (148, 164, systolic; and 118, 124, diastolic).

EXPERIMENTAL OBSERVATIONS

The following pertinent experimental observations were made over a period of three months:

1. On April 17, a control electrocardiogram showed a P-R interval of 0.08 second and a QRS time of 0.11 to 0.12 second. There was a notch on the upstroke of R_1, and also on the downstroke of R_2 at its summit. The heart rate was 68 to 75 per minute. Atropine sulfate (1.3 mg.) was given intravenously. Tracings were taken at short intervals for a period of fifteen minutes. The heart rate increased to 100 per minute. The voltage of the QRS complex increased in the standard leads. With the increase in voltage, the slur and notch on R_{1-2} were obliterated. The P-R interval and the duration of the QRS complex were not affected. Fifteen minutes after the administration of atropine, prostigmine methylsulfate (1 c.c. of 1:4,000 solution) was administered subcutaneously. Twenty minutes later the heart rate was 72. There was no other change in the electrocardiogram.

2. On April 17, 18, and 19, the patient was given a daily oral dose of 0.4 Gm. (4 cat units) of digitalis leaf. On April 20, the tracing showed his usual (abnormal) pattern in Leads I and II. In Lead III

there was an occasional altered (normal) beat, and, in Lead IV, regularly recurring complexes with a P-R interval of 0.16 second and a QRS time of 0.08 second were recorded. The RS-T$_4$ segment was elevated, and T$_4$ was diphasic. The record obtained April 21 is reproduced in Fig. 1, *A*, and that of April 22, in Fig. 1, *C*. This latter was the only record with reversed conduction relationships in all leads throughout the course of the observations except those obtained after the administration of quinidine.
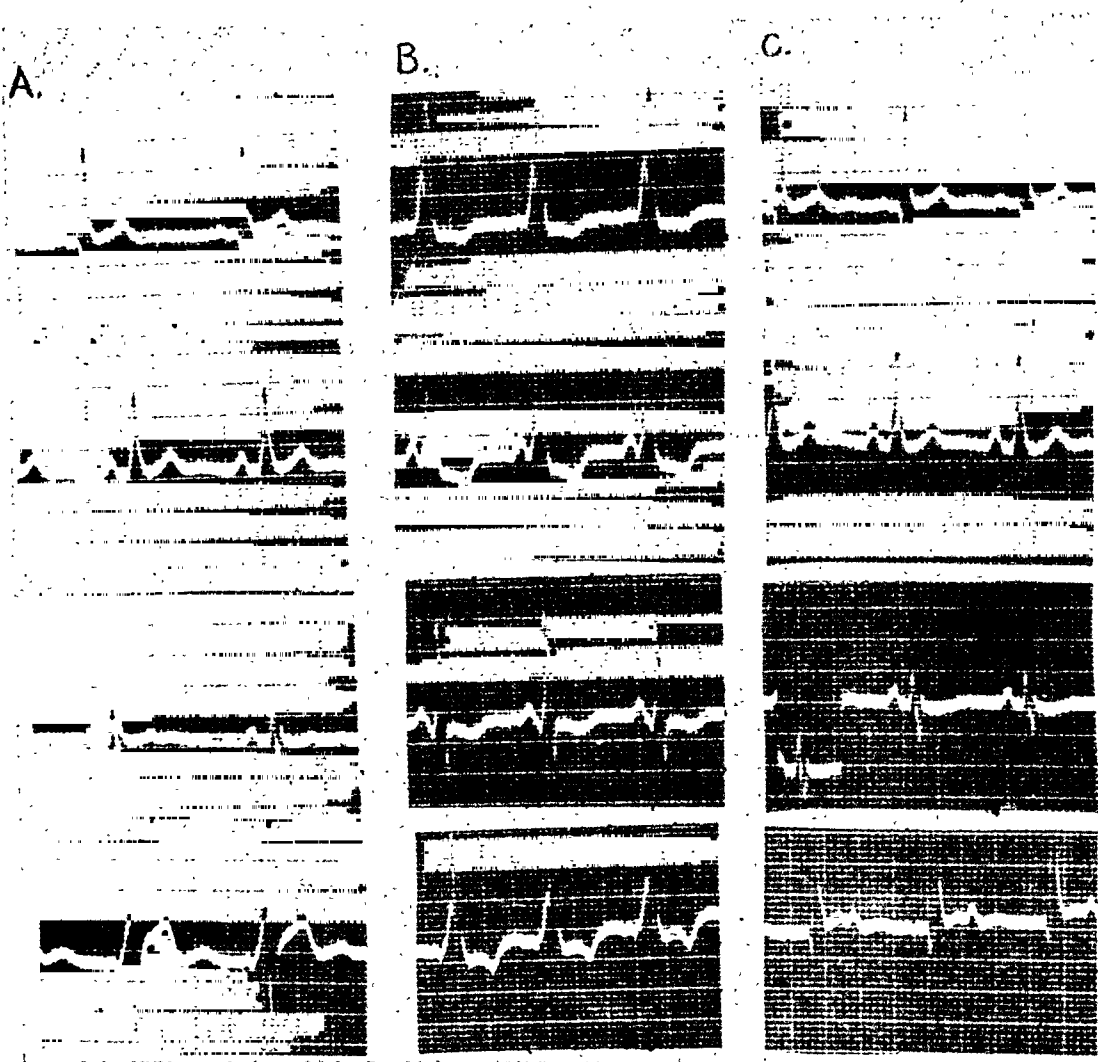
Fig. 1.—*A*, Leads I, II, and III show normal sinus rhythm. Lead IV shows a short P-R interval and a prolonged QRS complex. Lead IV differs, however, from the usual fourth lead in the abnormal tracings. *B*, The characteristic abnormal tracing. *C*, Normal sinus complexes in all four leads.

3. On April 24, 2 mg. of atropine sulfate were given intravenously. The heart rate increased from 75 per minute in the control record to 100 per minute. There was an increase in the voltage of the QRS complex in the standard leads, as observed previously after the administration of atropine. In a series of tracings taken over a period of twenty minutes, the rhythm remained the same. Twenty minutes after the administration of atropine, prostigmine methylsulfate (1 c.c. of 1:4,000 solution) was given intramuscularly. The heart rate decreased to 86 per minute with no other change.

4. On April 25, positional tracings were taken on deep inspiration and deep expiration. The electrocardiographic pattern remained abnormal in all tracings obtained. Structural changes occurred in the

R wave and in T_1. There were spontaneous variations in heart rate from 60 to 100 per minute. Some of the variations are recorded in Fig. 2.

5. Beginning April 30, the patient was given 0.4 Gm. (4 cat units) of digitalis leaf daily by mouth for four consecutive days. Daily electrocardiograms were secured. The only changes observed were exaggerated depression of the R-T segments in all leads and variations in rate (Fig. 3, B and C).

6. On May 8, the control tracing showed a heart rate of 75 per minute. R-$T_{1\ and\ 2}$ were still markedly depressed. Epinephrine (0.5 c.c. of a 1:1,000 aqueous solution) was administered intramuscularly. Tracings were obtained fifteen, twenty, and twenty-five minutes after the injection. Twenty minutes after the injection the heart rate was 50, which was the slowest rate ever observed in this case (Fig. 3, A).
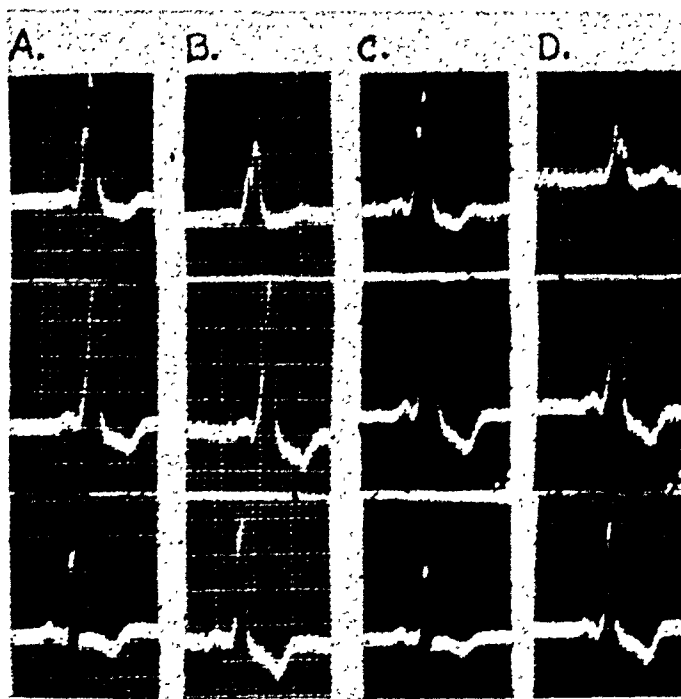
Fig. 2.—Positional tracings. A, Leads I, II, and III taken in the supine position. B, Leads I, II, and III taken in the supine position on deep inspiration. C, Leads I, II, and III taken in the right lateral position. D, Leads I, II, and III taken in the left lateral position.

7. On May 15, the control tracing showed a heart rate of 60 per minute. Mecholyl chloride (15 mg.) was given subcutaneously. A tracing obtained two minutes after the injection showed a rate of 100 and accentuation of the notch on the upstroke in Lead I, with concomitant lowering of the voltage of QRS_1, as if a change in the electrical axis had taken place. Seven minutes later, at the height of the systemic reactions due to mecholyl (sweating, lacrimation, and choking sensation), 2 mg. of atropine sulfate were given intravenously. The heart rate remained at 100 per minute, approximately the same as before the injection. The voltage of R_1 increased and the notch on the upstroke became less conspicuous. No other structural change in the electrocardiogram took place. An occasional premature ventricular contraction appeared.

8. On May 19, the patient was given an oral test dose of quinidine sulfate (0.2 Gm.), after which 0.4 Gm. was given orally every four hours. On May 20, he had 0.4 Gm. of quinidine at 8:00 A.M. and 0.8 Gm. at noon. In the two days he had received a total of 3.3 Gm. of the drug. An electrocardiogram taken at 3:00 P.M. showed a normal sinus pattern similar to the tracing reproduced in Fig. 1, C.

9. On May 22, the control tracing showed the usual (abnormal) characteristics. A single dose of 0.8 Gm. of quinidine sulfate was administered. A tracing obtained three and a half hours later again showed the normal sinus pattern.

10. On May 25, the control tracing showed the usual abnormality. Two and a half hours after a single dose of 0.8 Gm. of quinidine, a tracing revealed a normal pattern in all leads. At this time 4 c.c. of prostigmine methylsulfate (1:4,000) were given intramuscularly. A tracing taken fifteen minutes later was again abnormal. This took place approximately two hours and forty-five minutes after the administration of quinidine.
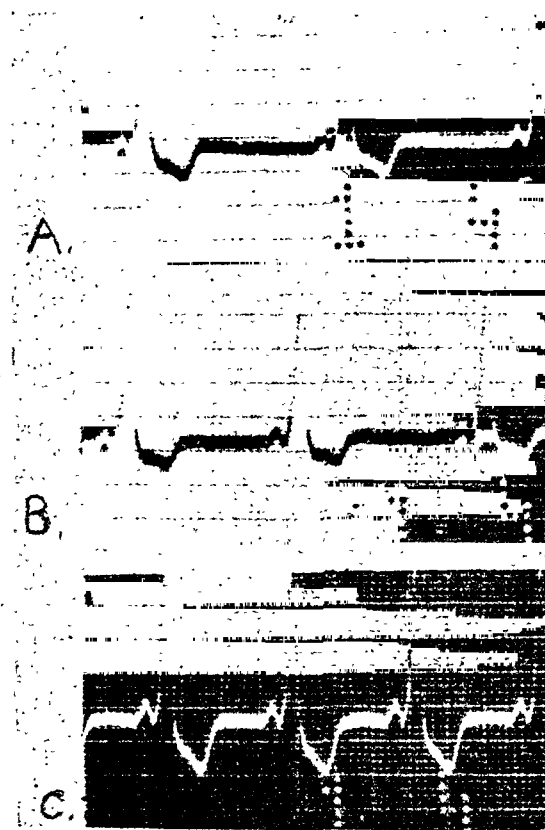
Fig. 3.—Lead II only. A, The effect of 0.5 c.c. of 1:1,000 epinephrine intramuscularly. B, Tracing taken after two daily doses of digitalis leaf, 0.4 Gm. each. C, Tracing taken after four daily doses of digitalis leaf, 0.4 Gm. each.

11. On May 27, control tracings were abnormal. A single dose of 0.8 Gm. of quinidine sulfate was given orally, and frequent tracings were taken in order to establish the time of onset and the duration of the expected change in conduction. It appeared two and a half hours after the administration of the drug and lasted two and a half hours thereafter.

12. On June 1, the control tracing was abnormal. A single dose of quinidine sulfate (0.8 Gm.) was given orally. Two hours later a tracing showed an alternating type of conduction (Fig. 4, A and B). The subsequent tracings were normal. Three hours and forty-five minutes

after the administration of quinidine (about one and a half hours after the onset of normal conduction), 4 c.c. of prostigmine methylsulfate (1:4,000) were given intramuscularly. The tracing taken fifteen minutes later was still normal. The next tracing, taken forty-five minutes after the injection of prostigmine, was abnormal.

A.

B.
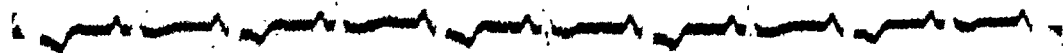
Fig. 4.—Alternating type of rhythm after quinidine. *A*, Lead II on one occasion. *B*, Lead III on another occasion.

13. On June 3, the control tracing was abnormal. Three hours after a single oral dose of quinidine sulfate (0.8 Gm.) the conduction was alternating. The three and one-half hour tracing was normal in all leads. Fifteen milligrams of mecholyl chloride were given subcutaneously about four hours after the administration of quinidine. Two minutes later the tracing still showed a normal conduction pattern, but the rate was faster. Ten minutes after the injection of mecholyl the conduction was alternating. At this point the systemic reactions due to mecholyl were so marked that atropine sulfate (1.2 mg.) was given intravenously. The tracing obtained immediately after the injection of atropine was again abnormal; the rate was slightly slower than in the control tracing. Fifteen minutes after the injection of atropine the rate was considerably slower than in the control (Fig. 5).

14. On June 4, the control tracing was abnormal. A single oral dose of 0.8 Gm. of quinidine sulfate was administered, and several tracings were taken at frequent intervals. The tracing was still abnormal three and a half hours after quinidine was given. It first became normal four hours after the administration of quinidine. Six cubic centimeters of digifolin (3 cat units) were then given intravenously. A tracing taken two minutes later was normal. Fifteen minutes after the injection of digifolin, the electrocardiogram was again abnormal. There was no other structural change in any of the segments of the QRS-T complex.

15. On June 5, quinidine (0.8 Gm.) again was given orally. A single tracing, obtained four hours later, showed normal conduction. The control had shown the usual abnormal characteristics.

16. On June 18, it seemed that the patient had become tolerant to quinidine. He was given 0.8 Gm. of the drug at 7:00 A.M. (before

breakfast). Frequent electrocardiograms were taken. Four hours and forty minutes after the administration of the drug, the tracing was still abnormal. He was given a second dose of 0.8 Gm. at 11:50 A.M. One hour later the electrocardiographic pattern was normal. At this time strophanthin K (0.25 mg. in 1 c.c.) was given intravenously. Serial tracings were taken immediately after the injection and for five hours subsequent to it. The conduction remained normal. No tracings were taken during the night. The following morning the conduction was again abnormal.
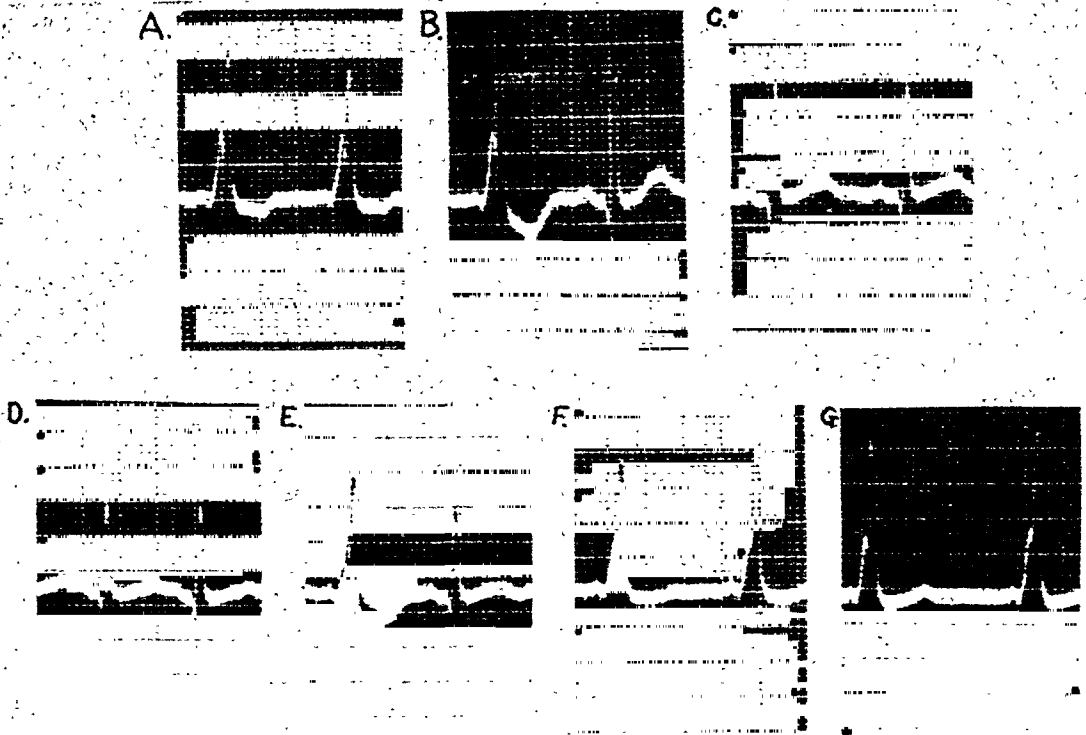
Fig. 5.—*A*, Control tracing. *B*, Alternating rhythm observed three hours after a single dose of quinidine (0.8 Gm.). *C*, Normal tracing three and one-half hours after administration of quinidine. *D*, Tracing obtained two minutes after 15 mg. of mecholyl subcutaneously. *E*, Alternating rhythm after injection of mecholyl. *F*, Abnormal tracing following injection of mecholyl. *G*, Tracing obtained fifteen minutes after injection of atropine. Note slow rate as compared with control tracing in *A*.

17. On June 22, four hours and fifteen minutes after a single dose of quinidine (0.8 Gm.), the electrocardiogram was still abnormal. A second dose of 0.4 Gm. was then administered. Forty-five minutes after the second dose the tracing was normal. Forty-five minutes later, strophanthin K (0.5 mg. in 10 c.c. of saline) was given intravenously. Tracings were taken at frequent intervals for one and one-half hours. The pattern remained normal. The next tracing, one hour later, was abnormal; it was taken two and one-half hours after the injection of strophanthin, or three hours and fifteen minutes after the conduction became normal.

18. Beginning June 25, the patient was given 0.4 Gm. of quinidine sulfate four times daily for a period of eight days. No medication was given during the night. Electrocardiograms were secured daily at about the same time (3:30 P.M.). A normal pattern was observed on one occasion only (June 30). The last two abnormal tracings showed an upright T_1.

19. On July 3, a single dose of quinidine sulfate (1.1 Gm.) was given at 7:00 A.M. A tracing secured at 10:30 A.M. was normal. Prostigmine

methyl sulfate (5 c.c. of 1:4,000 solution) was then administered intramuscularly. Tracings were taken at five-minute intervals. Fifteen minutes after the injection the patient appeared uncomfortable; his face was covered with beads of perspiration. The twenty-five-minute tracing was still normal, without even an appreciable change in the heart rate. Fifteen milligrams of mecholyl chloride were then administered subcutaneously. Two minutes later the heart rate increased from 70 to 120 per minute; the conduction, however, remained normal. Three minutes after the injection of mecholyl the patient's discomfort increased greatly. He perspired profusely, and developed a choking sensation and an intense desire to urinate. Two milligrams of atropine sulfate were immediately injected intravenously. Tracings were taken before, during, and after the injection. The conduction remained normal. The heart rate, however, decreased to 87 per minute within five minutes after the injection. Consecutive tracings at frequent intervals were normal until 2 P.M., when the first abnormal tracing was obtained (heart rate, 75 per minute). It differed from the control in that it showed extremely high voltage of the QRS complexes, apparently an effect of atropine, as observed previously.

COMMENT

During the three months the patient was under observation, 105 electrocardiograms were taken. On one occasion, a tracing showing normal sinus rhythm in all four leads was obtained three days after digitalis was discontinued. All other normal tracings apparently resulted from giving quinidine. Quinidine sulfate was given on twelve occasions; in doses of 0.8 Gm. or more it never failed to produce a normal sinus pattern. The effect of the drug was apparent as early as two hours after its administration. In the later observations (Experiments 16 and 17), a longer time was required for the effect to become manifest. It is quite possible that the element of time, rather than the second dose of the drug, was the determining factor in producing the normal electrocardiographic pattern in these experiments. The duration of the quinidine effect was at least two and one-half hours after a single dose of 0.8 Gm., and at least five hours when a second dose was given five hours after the unsuccessful, or insufficient, first dose. The effect of a single 1.1 Gm. dose was a normal conduction pattern which lasted at least three and one-half hours.

The effect of quinidine on this electrocardiographic phenomenon was previously reported by Roberts and Abramson.[6] Their observations were subsequently confirmed by Wolferth and Wood.[7] It is interesting that doses of 0.325 Gm. were ineffectual in the latter's case, whereas a double dose produced a normal pattern. It is evident that, in order to maintain the normal conduction pattern, large doses would have to be repeated at frequent intervals to balance the rate of absorption and the rate of excretion of the drug. The effect of quinidine is interesting from the physiologic point of view. It lends support to the hypothesis advanced by Holzmann and Scherf[2] and Wolferth and Wood[3] that the syndrome is due to the presence in some hearts of an aberrant conduction

mechanism which connects one of the auricles with one of the ventricles. Quinidine apparently has a pronounced affinity for the aberrant mechanism, and depresses it. Normal transmission of the sinus impulse then takes place through the A-V node, with the normal electrocardiographic pattern. On the other hand, any substance with a greater affinity for the A-V node will depress it and allow propagation of the sinus impulse through the aberrant mechanism, with the resulting abnormal electrocardiographic pattern.

The effect of digitalis on the syndrome was first noted by Scherf and Schönbrunner.[8] They observed an increase in the duration of the abnormal QRS complex after the administration of digitalis and ultimate disappearance of the abnormally conducted beats when the drug was continued. They concluded that the abnormal conduction mechanism is more susceptible to the effects of digitalis than the specific conduction tissue.

In a recent communication,[5] a more detailed study of the effect of digitalis on the syndrome was reported. An increase in the duration of the abnormal QRS complex was produced by the drug, and evidence was presented to indicate that the phenomenon is vagal in character. The effect of digitalis on the abnormal complex was interpreted as indicating increased asynchronism of ventricular stimulation due to the cholinergic properties of the drug, particularly to its depressing effect on the A-V node. The usual abnormal complex was thought to be a compromise effect of the simultaneous functional activity of the A-V node and the aberrant tissue.

In the case herewith presented, no such effect of digitalis on the abnormal complex was observed. When administered (intravenously), however, at a time when the aberrant conduction tissue was depressed and the conduction pattern was normal, it caused reappearance of the abnormal complex. Other cholinergic drugs, namely, prostigmine and mecholyl, had a similar action. Since the transformation of the normal conduction pattern to the abnormal one was accomplished soon after a normal pattern was established, it is hardly possible that this could have been spontaneous. The failure of the combined action of mecholyl and prostigmine to reproduce the abnormal pattern in Experiment 19 may be explained by the marked depression of the aberrant tissue caused by a large dose of quinidine (1.1 Gm.). The double dose of quinidine in Experiments 16 and 17 was probably the cause of the failure of strophanthin to produce the abnormal conduction pattern. The struggle between the A-V node and the aberrant tissue in this case did not result in a compromise modification of the QRS complex, but rather in a surrender of the functional activity of one or the other mechanisms.

The presence of exaggerated vagal tone in cases of this syndrome is supported by the following additional evidence: sinus arrhythmia of greater or lesser extent was almost universally present in all the abnormal tracings. The heart rate was subject to spontaneous fluctuations

from 60 to 100 per minute (Fig. 3, *B* and *C*). Even when the vagus was not in full control (Fig. 4), an arrhythmia manifested itself in the relation of the abnormal groups to the normal ones and also in their relationship to each other. After an injection of epinephrine, the patient behaved like an animal with its vagi intact; his heart slowed—a phenomenon supposed to be reflexly mediated through the carotid sinus and aortic nerves and caused by elevation of the blood pressure. The slowing of the heart rate produced by atropine after mecholyl is probably of the same nature, and is caused by the rise in blood pressure.

SUMMARY

A case of short P-R interval and prolonged QRS complex is presented.

On repeated occasions the abnormal electrocardiogram was transformed into a normal one by the oral administration of quinidine.

Cholinergic drugs, including digitalis, when administered soon after the appearance of the normal electrocardiographic pattern, reproduced the abnormal pattern.

These observations are in harmony with the hypothesis that the abnormal electrocardiographic pattern is due to an accessory auriculoventricular conduction mechanism. Quinidine sulfate apparently has a greater affinity for the accessory tissue, and depresses it, thus allowing transmission of the sinus impulse through the normal pathway, whereas the cholinergic drugs (including digitalis), by depressing the A-V node, divert the impulse through the aberrant conduction tissue.

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CLINICAL EXPERIENCE WITH DICUMAROL

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THE prothrombin-lowering principle of spoiled sweet clover, 3,3′-methylene-*bis*-(4-hydroxycoumarin), was isolated, identified, and synthesized by Link and his co-workers.[1-4] The synthetic preparation, dicumarol, was first used in man by Butt, Allen, and Bollman,[5] and by Bingham, Meyer, and Pohle.[6] Both groups of investigators suggested that giving small doses of the drug daily was more effective than a single large dose, and that dicumarol might be used as a substitute for heparin in the prevention of thrombosis. Meyer, Bingham, and Pohle[7] recommended an initial oral dose of 5 mg. per kg. of body weight, followed by 1 to $\frac{1}{5}$ mg. per kg. daily.

This report is based on the study of thirty patients with thromboembolic diseases (Table I). There were fourteen cases of peripheral arterial occlusion (six femoral, two popliteal, two axillary, one brachial, two thromboangiitis obliterans, one arteriosclerosis obliterans); one case of coronary artery occlusion; four cases of cerebral artery occlusion (two embolic, associated with rheumatic heart disease, and two thrombotic); two cases of subacute bacterial endocarditis; four cases of pulmonary artery occlusion; one case of retinal vein thrombosis; three cases of thrombophlebitis; and one case of what was probably hepatic vein thrombosis.

METHOD OF STUDY

Twenty-five patients received 300 mg. of dicumarol orally on each of the first two days, and 50 mg. daily thereafter. The drug was discontinued when the first indication of hemorrhage appeared. Five patients received 200 mg. every other day; the intervals were prolonged when the prothrombin was considered to be dangerously low. The average predosage levels were: plasma prothrombin, 80 per cent; clotting time, four minutes; bleeding time, two minutes. In all cases a control determination of plasma prothrombin, venous clotting time, and bleeding time were made just prior to the administration of dicumarol and at frequent intervals throughout the therapeutic period. In many cases, similar observations were made with respect to the leucocyte count, hemoglobin, blood sugar, blood urea nitrogen, van den Bergh, icterus index, bromsulfalein retention, and urine specific gravity, albumin, sugar, and formed elements.

Plasma Prothrombin.—Quick's[8] method was used for determining the plasma prothrombin, and the results were expressed in percentage of

TABLE I

SUMMARY OF PATIENTS TREATED WITH DICUMAROL

DIAGNOSIS	NUMBER OF CASES	RE-COVERED	DIED	CASE NUMBER	REMARKS
1. Peripheral arterial occlusion a. Femoral	6	×		1	Arteriosclerotic heart disease; auricular fibrillation; embolectomy; slight wound, bleeding on the third day; prothrombin, 20 per cent
		×		2	Gunshot perforation of femoral artery; massive hematoma; surgical repair; no toxicity
			×	3	Arteriosclerotic heart disease; died within twenty-four hours
			×	4	Arteriosclerotic heart disease; diabetes mellitus; no toxicity
		×		5	Gangrene of toes (body cast for fractured femur); 200 mg. every other day for 34 doses; improved circulation; no toxicity
		×		6	Gangrene of toe; 200 mg. every other day; no toxicity
b. Popliteal	2	×		7	Gangrene of toes; amputation; no toxicity
		×		8	Slight circulation improvement; no toxicity
c. Brachial	1	×		9	Arteriosclerotic heart disease; gangrene on tips of two fingers; slow improvement; rectal bleeding on twelfth day; prothrombin, 11 per cent; clotting time, five minutes
d. Axillary	2	×		10	Rheumatic heart disease; auricular fibrillation; 200 mg. every other day; no toxicity
			×	11	Arteriosclerotic heart disease; heart block; diabetes mellitus; died within twenty-four hours; no toxicity
e. Thromboangiitis obliterans	2	×		12	Slight temporary improvement; leg amputation later; no toxicity
		×		13	Slight improvement in one leg; 200 mg. every other day for three weeks; no toxicity
f. Arteriosclerosis obliterans	1	×		14	No improvement, leg amputation later; no toxicity
2. Coronary artery occlusion	1		×	15	Died on nineteenth day; prothrombin, 100 per cent at death; no toxicity
3. Cerebral artery occlusion a. Embolic	2	×		16	Rheumatic heart disease; congestive failure, no toxicity
		×		17	Rheumatic heart disease; auricular fibrillation; slow improvement; small episcleral hemorrhage on sixth day; bleeding time six minutes; clotting time, six minutes; prothrombin 8 per cent

TABLE I—CONT'D

DIAGNOSIS	NUMBER OF CASES	RE-COVERED	DIED	CASE NUMBER	REMARKS
b. Thrombotic	2	*		18	Hypertensive heart disease; diabetes mellitus; slow improvement; no toxicity
			*	19	Died in four days; blood not clotted at autopsy table, twelve hours after death
4. Subacute bacterial endocarditis	2		*	20	Died after two months' treatment; no toxicity
			*	21	Died in three days; no toxicity
5. Pulmonary artery occlusion	4	*		22	Auricular fibrillation; no toxicity
		*		23	Secondary to phlebitis; no toxicity
		*		24	Following cesarean section; hematuria and vaginal bleeding on eighth day; prothrombin, 8 per cent; clotting time, ten minutes; one blood transfusion
		*		25	Small hemorrhages of feet two weeks after treatment begun; prothrombin 47 per cent; 200 mg. every other day for thirty-five days
6. Retinal vein thrombosis	1	*		26	Progressive improvement; no toxicity
7. Thrombophlebitis	3	*		27	Pelvic inflammatory disease, phlebitis of leg; improved rapidly; no toxicity
		*		28	Prompt improvement; no toxicity
		*		29	Good results; no toxicity
8. Hepatic vein thrombosis	1	*		30	Acute phlebitis of leg twelve days post partum; enlarged liver; abdominal distention; prominent superficial abdominal veins; 200 mg. every other day; no toxicity
Totals	30	23	7		

the average normal. Acetone-treated rabbit brain served as thromboplastin, and, with normal plasma, gave prothrombin times of eleven to thirteen seconds.

Venous Clotting Time.—Five cubic centimeters of venous blood were withdrawn into a sterile, dry syringe and quickly transferred to a chemically clean, dry test tube which was gently tilted every thirty seconds until the entire sample no longer flowed. The venous clotting time was recorded as the time which elapsed from the moment the blood was shed to when it congealed.

Bleeding Time.—The finger tip was pricked, and the time the drop of blood took to clot sufficiently to close the puncture in the skin and stop the bleeding was noted. The moment when bleeding ceased was taken as the end point.

RESULTS

Of the thirty patients treated, twenty-three recovered and seven died (Table I). Analysis of the deaths reveals that no toxic manifestations due to the drug were observed in any. Two were treated for femoral artery occlusion, one for axillary artery occlusion, one for coronary

artery occlusion, one for cerebral thrombosis, and two for subacute bacterial endocarditis. It is difficult to say whether or not the dicumarol contributed to the fatal outcome in any of these. It is our impression, however, that the disease pursued its natural course. It is equally difficult to credit the drug with contributing to recovery in our cases with a favorable outcome, although evidence is extant in this direction. Observations on the peripheral circulation were made by one of us (D. W. K.[9]). Oscillometric readings were made in eight cases; in five there was slight improvement, and in three, no appreciable effect on the larger arteries. In one case, there was definite improvement on the uninvolved side. With the histamine test, six of the eight patients showed improvement, two of whom showed definite improvement in the peripheral circulation by capillary response. When the larger arterial trunks are involved with thrombotic formation, the oscillometer will usually not demonstrate much improvement unless an appreciable amount of arteriospasm is present. The histamine test, however, is more likely to detect improvement in the distal capillary circulation.

Prothrombin.—Fig. 1 represents the results of determinations of plasma prothrombin in terms of percentage of normal in the patients who received 300 mg. daily for two days and 50 mg. daily thereafter. Three patients received dicumarol for as long as forty-four, fifty, and fifty-three days, respectively, with no evidence of cumulative or toxic effect. The curve which rises rapidly to a sustained prothrombin level of 100 per cent (Case 15) is difficult to interpret. Considering expected effect, the probable explanation for this is failure of absorption of the drug.

The broken line shows prompt restoration of the prothrombin eight days after withdrawal of the drug, which began when the prothrombin was 8 per cent (Case 24). One blood transfusion was given. In four cases, the prothrombin dropped to less than 10 per cent of normal, and transient hemorrhage occurred in two of these (Cases 17 and 24).

Fig. 2 (curve A) is a composite derived from a spot graph of Fig. 1. Although it fails to indicate the indubitably present latent period (because of insufficient determinations of prothrombin after twenty-four hours of treatment), it shows a rapid reduction of the prothrombin to a level of 25 to 30 per cent in two to three days, a maximum reduction in four to seven days, and then a slow, progressive rise to a level of about 50 per cent in four weeks, where it was subsequently maintained. The prothrombin was 20 per cent or less from the fourth to the ninth days.

Clotting Time.—Fig. 3 shows the results of the various clotting time determinations. These vary less markedly than do the prothrombin changes. The single clotting time of twelve minutes is associated with a prothrombin of 18 per cent, and the one of ten minutes with a prothrombin of 8 per cent. The broken line represents the return to a normal clotting time level of four minutes, eight days after cessation of the drug (Case 24). This is in general agreement with the observations of Quick,[10] who found the coagulation time relatively little delayed until
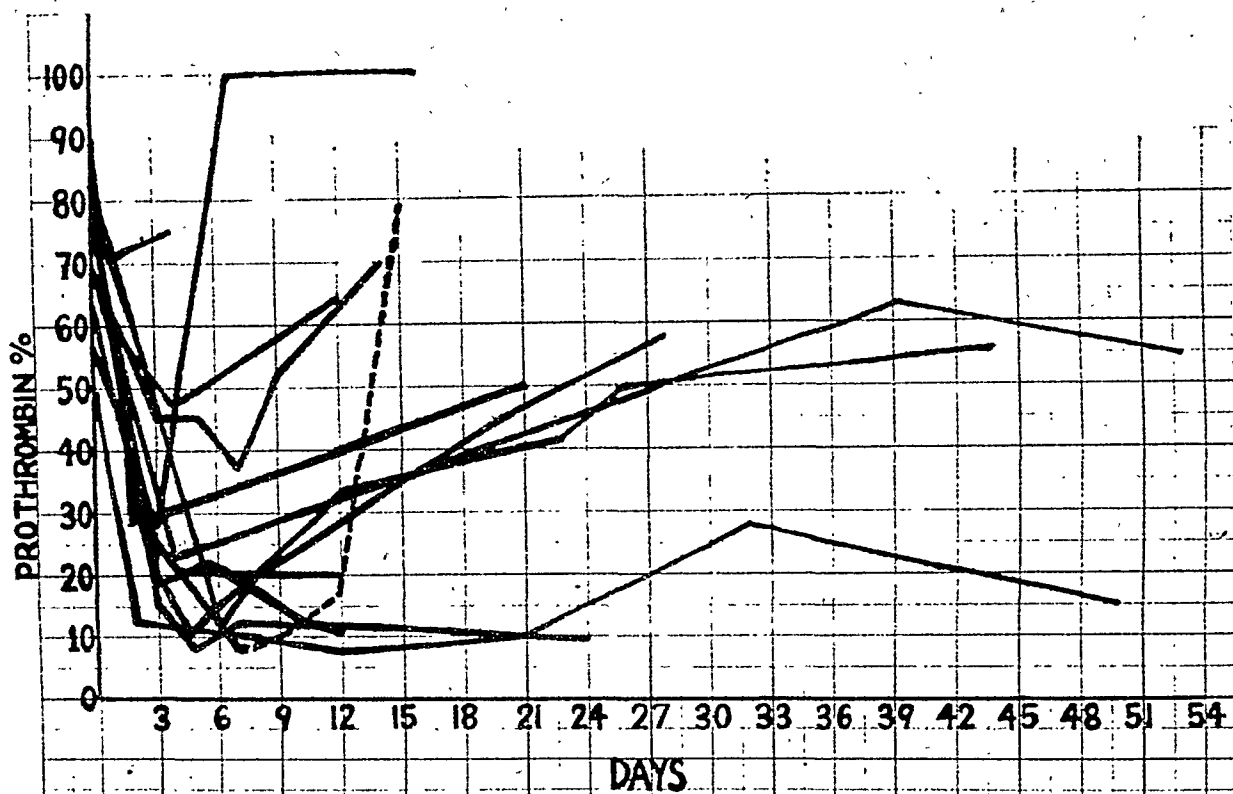
Fig. 1.—Prothrombin determinations during oral dicumarol dosage of 300 mg. daily for two days, followed by 50 mg. daily. The broken line (Case 24) represents prothrombin percentage after cessation of dicumarol therapy and one blood transfusion.
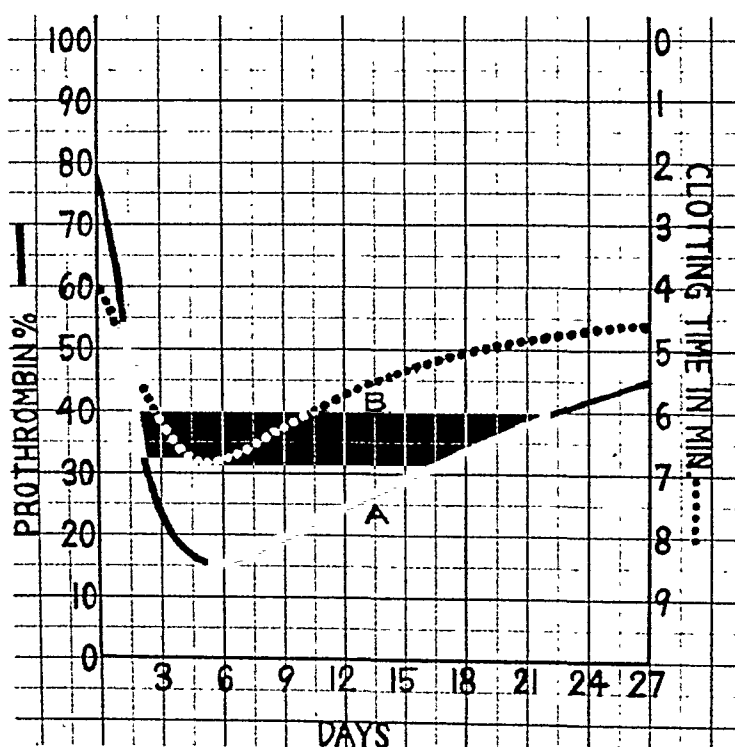
Fig. 2.—Comparison of composite curves of prothrombin percentage and clotting time (obtained from spot graphs of Figs. 1 and 3 respectively), showing quantitative difference and close parallel.
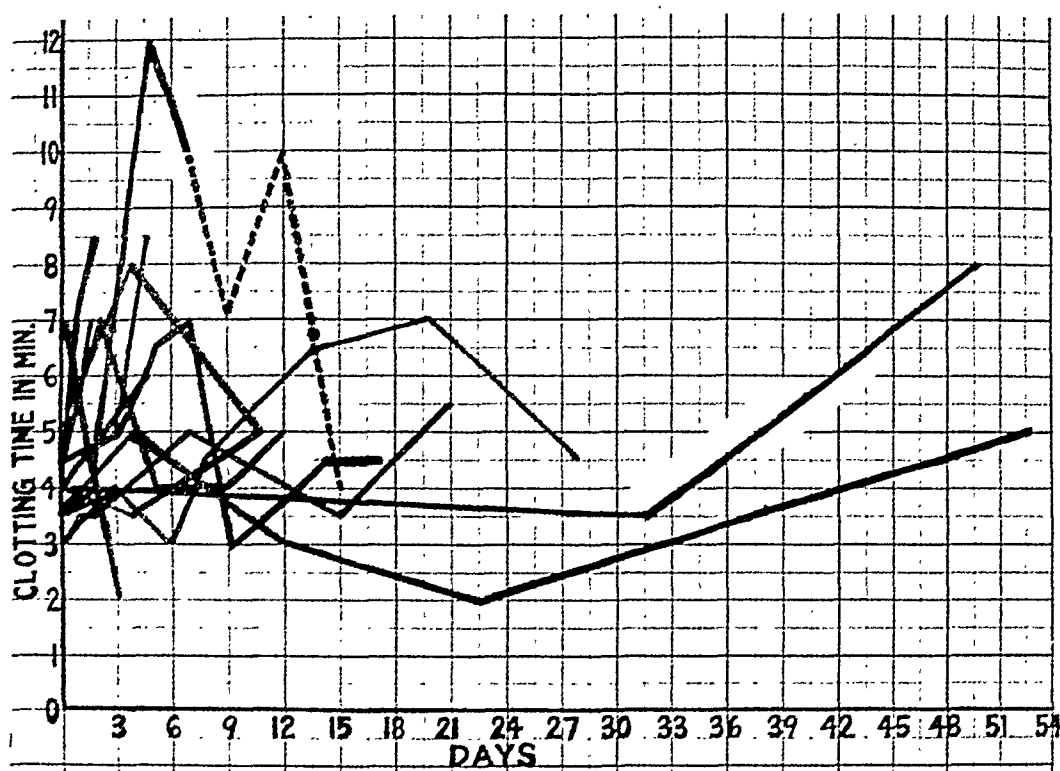
Fig. 3.—Clotting time determinations during the study. The broken line (Case 24) represents determinations after cessation of dicumarol therapy and one blood transfusion.
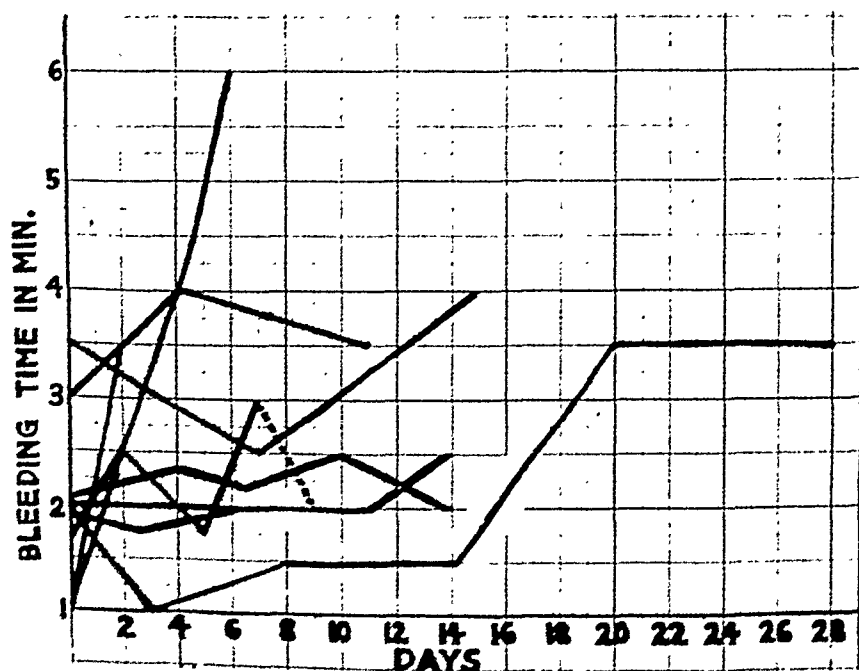
Fig. 4.—Bleeding time determinations, showing, by inspection, lack of significant alterations.

the prothrombin content dropped below 20 per cent of normal. Barker, Butt, Allen, and Bollman[11] reported that an increase in coagulation time usually occurred, but was considerably less constant than the effect on the prothrombin time.

Fig. 2 (curve *B*) is a composite of Fig. 3, and shows a rapid increase in clotting time to a level of six minutes in two to three days, a maximum increase from four to seven days, and then a gradual return to a level slightly greater than normal in about four weeks. The clotting time is six minutes or more from the third to the tenth days. This curve parallels the prothrombin curve rather closely (Fig. 2).

Bleeding Time.—The results of the bleeding time determinations (Fig. 4) are very variable. No pathologic level was observed, except the one of six minutes, at which time the prothrombin was 8 per cent (Case 17). This conforms with the observations of Allen, Barker, and Waugh[12] that the bleeding time is not influenced by dicumarol, and with those of Wright and Prandoni[13] that there is considerable variation in the bleeding time.

<div align="center">TOXICITY</div>

No changes attributable to the dicumarol were observed in the leucocyte count, hemoglobin, blood sugar, blood urea nitrogen, van den Bergh, icterus index, bromsulfalein retention, and urine specific gravity, albumin, sugar, and formed elements. The effect on plasma prothrombin, venous clotting time, and bleeding time have been discussed. Schofield[14] found that spoiled sweet clover produced no abnormality of calcium or fibrinogen. No increase in antithrombin or decrease in platelets was noted by Roderick.[15] Quick[10] observed no alteration in any coagulation factor except prothrombin. Allen, Barker, and Waugh[12] reported an increased sedimentation rate and retarded clot retraction as a result of dicumarol. The latter observation was confirmed by Wright and Prandoni,[13] who, however, found no sedimentation rate changes, no increase in capillary fragility, and no hepatic or renal damage. Butt, Allen, and Bollman[5] reported no change in hemoglobin, erythrocyte count, leucocyte count, erythrocyte fragility, blood typing, serum bilirubin, or urine. Davidson and MacDonald[16] noted no alteration in plasma proteins.

The only toxic manifestations in our series were hemorrhagic phenomena (Table II) in five cases. On the third day after leg amputation, slight wound bleeding occurred (Case 1). Although the prothrombin was 20 per cent at this time, the complication may have been coincidental. Rectal bleeding occurred on the twelfth day of treatment for brachial artery occlusion (Case 9). The prothrombin was 11 per cent, and the clotting time, five minutes. A small episcleral hemorrhage developed (Case 17) on the sixth day of treatment, at which time the prothrombin was 8 per cent, the clotting time, six minutes, and the bleeding time, six minutes. On the eighth day after cesarean section (Case 24), hematuria

TABLE II

Toxicity of Dicumarol

CASE NUMBER	HEMORRHAGIC MANIFESTA- TION	DAY OF APPEAR- ANCE	PROTHROMBIN (%)	CLOTTING TIME (MIN.)	BLEEDING TIME (MIN.)
1	Postamputation wound bleeding	3	20	--	--
9	Rectal bleeding	12	11	5	--
17	Small episcleral hemorrhage	6	8	6	6
24	Postcesarean section hematuria and vaginal bleeding	8	8	10	3
25	Small hemorrhagic extravasations of feet	14	47	--	--

and vaginal bleeding occurred. The prothrombin was 8 per cent, the clotting time, ten minutes, and the bleeding time, three minutes. Small hemorrhagic extravasations on both feet developed on the fourteenth day, when the prothrombin was 47 per cent (Case 25). All five patients recovered promptly; dicumarol was discontinued immediately after evidence of toxicity was discovered. The patient with the hematuria and vaginal bleeding improved more slowly than the others, and required a whole blood transfusion.

Although the basic causative factor in the bleeding is defective coagulation due to prothrombin reduction, a possible added factor may be the extensive dilatation of small vessels noted by Bingham, Meyer, and Pohle[6] in animals which were receiving fatal doses of dicumarol. Duration of treatment is not a factor in toxicity, as indicated by the absence of ill effect in the three patients of our series who received the drug continuously for six to seven weeks. As much as 10 Gm. of dicumarol have been given over a ninety-two-day period without detectable changes in liver function.[17]

COMMENT

Since the risk of hemorrhage becomes distinct when the prothrombin is 20 per cent or less, it seems desirable to avoid the danger zone, from the third to ninth days (Fig. 2), by employing less drug during the first two days. The rising portion of the prothrombin curve might be explained by an increased tolerance to the drug, but it seems more reasonable to attribute it to the fact that the maintenance dose was approximately 1 mg. per kg., rather than the recommended 1.5 mg. per kg. The progressive increase in prothrombin to a level of 50 per cent seems undesirable because of the associated reduction in clotting time to an almost normal level.

A better dosage regime, therefore, might be 300 mg. of dicumarol on the first day, and 100 mg. thereafter. Although this schedule might produce a prothrombin curve more closely approximating the desired

one than does the authors' curve, it must be realized that, at best, it is only a rough guide toward dosage, and that the only reliable method of adjusting the daily dicumarol dose is by the results of frequent plasma prothrombin determinations.

There are a few large series reported on the use of dicumarol in normal persons to prevent thrombosis and embolism postoperatively,[11, 12, 18, 19] and several small series on the use of dicumarol in thrombo-embolic diseases.[11, 13, 20, 21] As with our results, the majority of reports are encouraging. Most investigators are agreed upon the absence of effect of dicumarol on the liver, kidney, or blood, except for the significant effect on prothrombin and clotting time. Hemorrhagic phenomena have been the only form of toxicity reported in man.

An obvious question which arises is, can the reduction of plasma prothrombin, particularly with the less marked alteration of venous clotting time, actually prevent intravascular clotting? There is experimental evidence for an affirmative answer. Allen, Barker, and Waugh[12] and Wright and Prandoni[13] observed retardation of clot retraction after dicumarol therapy. Bollman and Preston[22] noted a definite reduction in the tendency to thrombosis in glass cannulae inserted into carotid and femoral arteries of dicumarolized dogs. Dale and Jaques[23] made similar observations in veins crushed on a linen thread and in glass cells inserted between carotid artery and jugular vein. Richards and Cortell[24] found marked inhibition of thrombus formation in veins into which a sclerosing solution had been injected.

Contraindications to the use of dicumarol:

1. Subacute bacterial endocarditis, when there is already a natural tendency toward hematuria and central nervous system bleeding.[12]

2. Renal insufficiency, especially with urinary suppression. In this situation there is an exaggerated response to dicumarol.[12]

3. Blood dyscrasia in which the hemorrhagic diathesis is already present.

4. Liver damage with vitamin K deficiency, when the prothrombin concentration is already reduced and difficult to restore,[12, 19] and the effect on the prothrombin is more marked than in a patient without liver disease.[25]

5. Ulcerating or granulating lesions, because of the tendency to bleeding in such cases.[11, 18]

Indications for dicumarol:

1. To prevent postoperative thrombosis and embolism.

2. To prevent extention of a thrombus already formed, and, secondarily, improve blood circulation.

Disadvantages of dicumarol:

1. Start of the action is delayed twenty-four hours or more. This may be overcome by using heparin for the first thirty-six hours, until the full effect of dicumarol has developed.[17, 26, 27]

2. Increased clotting time persists several days after cessation of dicumarol therapy, and can be corrected only temporarily by blood transfusion.

3. Factor of capillary dilatation. This is probably not of practical importance because it was demonstrated only in animals which received a massive, fatal dose of the drug.

4. Prothrombin must be dangerously low before the clotting time is sufficiently altered. Therefore, facilities must be available for carrying out the frequent prothrombin determinations that are essential for safe regulation of the dicumarol dosage.

Advantages of dicumarol over heparin:

1. Effective when given by mouth.
2. Prolonged action.
3. Low cost.

SUMMARY

1. Thirty patients with thrombo-embolic diseases were treated with dicumarol.

2. No changes were observed in the leucocyte count, hemoglobin, blood sugar, blood urea nitrogen, van den Bergh, icterus index, bromsulfalein retention, and urine specific gravity, albumin, sugar, and formed elements.

3. On the dosage schedule of 300 mg. orally for two days and 50 mg. daily thereafter, the plasma prothrombin fell rapidly from 80 per cent to 25 per cent of normal in three days, was 20 per cent or less from the fourth to ninth days, and then rose slowly to a level of 50 per cent in four weeks, where it was subsequently maintained. Coincidentally, the clotting time rose from four minutes to a level of six minutes in three days, was six minutes or more from three to ten days, and then fell slowly to a level slightly greater than normal in four weeks. The bleeding time was uninfluenced.

4. Of the thirty patients, seven died and twenty-three recovered. Improvement in the peripheral vascular circulation was demonstrated in six of eight cases studied.

5. Hemorrhage, the sole manifestation of toxicity, was observed in five cases, in all of which the patient recovered.

6. The only reliable method of ascertaining the proper dose of dicumarol is by frequent plasma prothrombin determinations.

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ALTERATIONS IN THE FORM OF THE T WAVES WITH CHANGES IN HEART RATE

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A LTERATIONS of the ventricular electrocardiogram appear occasionally in the first normal beat which follows an extrasystole. When a conduction disturbance exists in one of the bundle branches, the long postextrasystolic pause may permit better recovery of the specific tissue, thus improving the conduction of the first postextrasystolic beat. The signs of intraventricular block may disappear from this ventricular complex in the electrocardiogram.[5, 16] Variations of the first postextrasystolic T wave are also encountered after interpolated ventricular extrasystoles; the recovery time for the first postextrasystolic beat is too short, and the stimulus for the first ventricular contraction after the extrasystole spreads aberrantly within the ventricles. In such instances, changes are usually also seen in the QRS complex. Finally, after a long series of extrasystoles (paroxysmal tachycardia), T-wave changes may be found for a short time;[3] they can be explained by the cardiac damage caused by the tachycardia (anoxia, exhaustion).

This paper deals with alterations of the T waves and of the S-T segments which appear in the first postextrasystolic beat after single extrasystoles and without changes of the QRS complex. Hitherto they have rarely been observed, and have not, to our knowledge, received detailed study.

Electrocardiograms made at the Metropolitan Hospital during the years 1940 to 1942 constituted the material used in this investigation. In these three years, 16,810 tracings were taken. Occasionally more than one electrocardiogram was made on the same patient. In the Medical Department, an electrocardiogram was recorded routinely on every patient; in the other departments this happened only if an arrhythmia was discovered or a heart lesion suspected. The number of older patients in this hospital population is somewhat higher than in most general hospitals.

Extrasystoles were found in 168 cases, that is, in one per cent of the electrocardiograms taken. Changes in the final deflection of the first postextrasystolic beat were seen in 57 cases, or one-third of those with extrasystoles. Among these 57 patients, 14 had auricular, and 43 ventricular, extrasystoles. In 15 cases, the electrocardiogram was otherwise normal, or showed only left axis deviation. In the others the changes varied. The pattern of left ventricular strain (left axis devia-

tion with displacement of S-T segment and T waves in a direction opposite to the main deflection) was seen frequently. Some patients showed the classical pattern of anterior wall infarction, others had inverted T waves in Lead I or II, and a few showed widening or splitting of the QRS complexes.
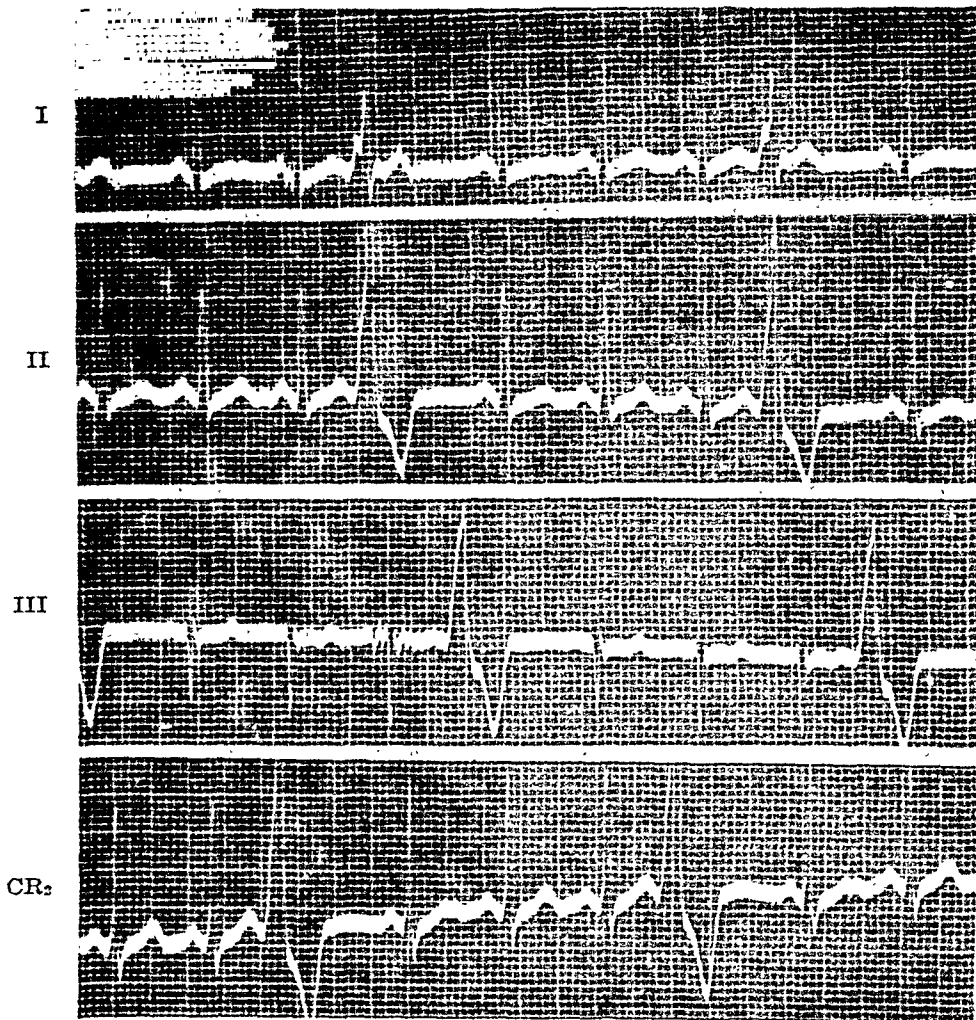
Fig. 1.—Ventricular extrasystoles in a case of left axis deviation; there are changes in the form of the T wave in the first postextrasystolic beat.

Some of the data collected from the 57 patients with changes in the T waves of the first postextrasystolic beat are shown in Table I. The first column gives the number; the second, the age of the patient; the third states the type of extrasystoles found; and the fourth indicates in which lead a postextrasystolic beat was registered. (Since all of the tracings were routine electrocardiograms, extrasystoles were frequently not registered in all leads.) The fifth column notes the presence or absence of evidence of organic heart disease, and the chief electrocardiographic findings are mentioned in the sixth. In the seventh column the changes in the T waves of the first postextrasystolic beat are described.

Fig. 1 was taken from a 32-year-old patient with hypertension (Case 50 of Table I). The electrocardiogram shows sinus tachycardia, with a

TABLE I

NUMBER	AGE (YR.)	TYPE OF EXTRA-SYSTOLES	LEAD IN WHICH POST-EXTRASYSTOLIC T WAVES WERE VISIBLE				PRESENCE OF ORGANIC HEART DISEASE	CHIEF FINDINGS IN THE ELECTROCARDIOGRAM	TYPE OF CHANGES IN THE POST-EXTRASYSTOLIC T WAVES
			I	II	III	C			
1	55	Ventricular	+	+	+	0	No	Left axis deviation	Positive T waves in Leads I and II are higher; negative T in Lead III is more negative
2	42	Ventricular	+	+	+	+	Yes	Left ventricular strain	No changes in limb leads; positive T in chest lead is diphasic
3	56	Auricular	+	+	+	+	Yes	Marked changes in QRS complex and T waves	Negative T in Leads I and II is more negative, positive T in Lead III is higher, positive T in chest lead is deep negative
4	73	Auricular	+	+	+	+	Yes	Left axis deviation, prolonged P-R	Positive T in Lead I is higher, negative T in Lead III is more negative
5	52	Ventricular	0	+	0	0	Yes	Anterior wall infarction	Positive T in Lead II is lower
6	36	Auricular	+	+	+	0	Yes	Anterior wall infarction	Flat T in Leads II and III becomes higher
7	72	Auricular	+	+	0	+	Yes	Left ventricular strain	Negative T in Lead I is positive, low T in Lead II is higher, positive T in chest lead is much higher
8	35	Ventricular	0	0	0	+	Yes	Normal	Positive T in chest lead is lower
9	61	Auricular	0	+	0	0	No	Normal	Positive T in Lead II is higher
10	56	Ventricular	0	+	+	0	Yes	Left ventricular strain	Negative T in Leads II and III becomes much more negative
11	71	Ventricular	+	+	+	+	Yes	Left ventricular strain	Negative T in Leads II and III is less negative; positive T in chest lead is lower
12	38	Ventricular	0	0	+	0	Yes	Anterior wall infarction	Negative T in Lead III is less negative
13	82	Auricular	+	+	-	+	Yes	Posterior wall infarction	Negative T in chest lead is positive
14	80	Ventricular	+	+	+	+	Yes	Left ventricular strain	Positive T in chest lead is negative

No.	Rate								Diagnosis	T wave description
15	80	Ventricular	+	+	+	+	+	Yes	Left ventricular strain	Negative T in Lead I is positive, positive T in Lead III is negative, positive T in chest lead is lower
16	79	Ventricular	0	+	0	0	0	Yes	Left ventricular strain	Flat T in Lead II is negative
17	60	Ventricular	+	+	+	+	+	No	Left axis deviation	Positive T in Leads I and II is lower, negative T in Lead III is positive, positive T in chest lead is lower
18	60	Ventricular	+	+	+	+	+	No	Left axis deviation	Positive T in Leads II and III is lower
19	62	Ventricular	0	+	0	0	0	Yes	No T in Lead I	Positive T in Lead II is much lower
20	80	Ventricular	0	0	+	+	+	Yes	Negative T in Leads I and II	Negative T in Lead III is positive, positive T in chest lead is lower
21	8	Auricular	+	+	+	+	+	No	Normal	Positive T in Leads I and II is higher, diphasic T in chest lead is negative
22	66	Ventricular	+	+	+	+	+	Yes	Abnormal T in Leads I and II	Very low T in Leads I and II becomes negative, positive T in chest lead is lower
23	45	Ventricular	+	+	+	+	+	Yes	Normal	Positive T in Lead I is negative, negative T in Lead III is positive
24	46	Ventricular	+	+	+	+	+	Yes	Abnormal QRS complexes and T waves	S-T depression is more marked and positive T in Lead II is lower
25	67	Ventricular	+	0	0	0	0	Yes	Left axis deviation, low T in Lead I	Low T in Lead I is negative
26	52	Ventricular	0	0	0	0	+	Yes	Marked changes	Positive T in chest lead is much higher
27	75	Auricular	+	+	+	+	+	Yes	Left ventricular strain	Negative T in Lead I is positive, positive T in Lead III is negative, positive T in chest lead is higher
28	56	Ventricular	+	+	+	+	+	Yes	Left ventricular strain	Depression of S-T in Lead I disappears, positive T in Leads I and II is lower
29	56	Ventricular	+	0	+	+	+	Yes	Left ventricular strain	Negative T in Lead I is deeper, positive T in Lead III is higher
30	38	Ventricular	+	+	+	+	0	Yes	Low T in Lead I, no T in Lead II	Low T in Lead I disappears, T in Leads II and III is negative

Table I—Cont'd

NUM-BER	AGE (YR.)	TYPE OF EXTRA-SYSTOLES	LEAD IN WHICH POST-EXTRASYSTOLIC T WAVES WERE VISIBLE				PRESENCE OF ORGANIC HEART DISEASE	CHIEF FINDINGS IN THE ELECTROCARDIOGRAM	TYPE OF CHANGES IN THE POST-EXTRASYSTOLIC T WAVES
			I	II	III	C			
31	52	Ventricular	+	+	+	0	Yes	Normal	Positive T in Leads I and II is lower, negative T in Lead III is less negative
32	66	Ventricular	+	0	+	0	Yes	Left ventricular strain	Negative T in Lead I is low positive
33	89	Ventricular	+	0	0	0	Yes	Left axis deviation	Positive T in Lead I is higher
34	71	Auricular	+	+	+	0	Yes	Left ventricular strain	T in Leads II and III is lower
35	69	Ventricular	+	+	+	+	Yes	Left ventricular strain	Negative T in Lead I is less negative, positive T in Lead II is negative, positive T in Lead III is much lower, positive T in chest lead is negative
36	84	Ventricular	0	+	+	0	Yes	Normal	Positive T in Leads II and III is lower
37	52	Auricular	+	+	+	+	Yes	Negative T in each lead	Negative T in Lead I is less negative, T in Lead II is invisible, negative T in Lead III is less negative, negative T in chest is positive
38	65	Auricular	+	+	+	0	Yes	Normal	Positive T in Lead I is lower, negative T in Lead III is higher
39	73	Ventricular	+	+	+	+	Yes	Left ventricular strain	S-T segment in Leads I and II is more depressed
40	48	Ventricular	+	+	0	0	Yes	Low T waves	T in Leads I and II is higher
41	52	Ventricular	+	+	+	0	Yes	Normal	Positive T in Leads I and II is higher, positive T in Lead III is negative
42	65	Ventricular	0	0	+	+	Yes	Normal	T in Lead III and chest lead is lower
43	29	Ventricular	+	+	+	+	Yes	Abnormal T waves	Negative T in Lead II becomes positive, positive T in Lead III is higher, negative T in chest lead is more negative
44	83	Auricular	+	+	+	+	Yes	Left ventricular strain	Negative T in Leads I and II is less negative, T in Lead III is higher, positive T in chest lead is higher

No.	Rate	Type					Reaction	Diagnosis	Description
45	78	Ventricular	+	+	+	0	Yes	Normal	Positive T in Leads I and II is lower, negative T in Lead III is more negative
46	63	Auricular	+	+	+	+	Yes	Left ventricular strain	Depressed S-T in Lead I is higher
47	46	Ventricular	+	+	+	0	Yes	Low T in Lead I	T in Leads I and II is lower
48	38	Ventricular	+	0	+	0	Yes	Negative T in Leads I and II	Negative T in Lead I is less negative, positive T in Lead III is lower
49	54	Ventricular	0	+	0	+	No	Normal	Positive T in Lead II is much higher, positive T in chest lead is lower
50	32	Ventricular	+	+	+	+	Yes	Left axis deviation low T in Lead I	Positive T in Lead I is isoelectric, positive T in Lead III is higher, positive T in chest lead is lower
51	70	Auricular	+	+	+	0	Yes	Abnormal T waves	Positive T in Lead I is negative, positive T in Lead III is higher
52	62	Ventricular	0	+	+	0	Yes	Low T in Lead I	Positive T in Leads II and III is higher
53	68	Ventricular	+	+	+	0	Yes	Left ventricular strain	Low T in Lead I is positive, positive T in Lead II is higher, positive T in Lead III is negative
54	57	Ventricular	+	0	0	+	Yes	Left ventricular strain	Positive T in Lead I is lower, positive T in chest lead is lower
55	60	Ventricular	+	+	+	0	Yes	Left ventricular strain	Low T in Leads I, II and III becomes lower
56	71	Ventricular	0	0	0	+	Yes	Negative T waves	Negative T in chest lead is positive
57	41	Ventricular	+	+	+	0	Yes	Normal	Positive T in Lead I is lower, positive T in Lead III is higher

heart rate of 110 and left axis deviation, without other changes in the QRS complexes. The T waves are positive in each lead, but rather low in Lead I. A ventricular extrasystole appears after every second or third beat. In Lead I the T waves of the first postextrasystolic beat become lower and slightly diphasic. The T wave in Lead II also becomes flattened after the extrasystole; in Lead III it is higher for the one beat after the extrasystole, and, in Lead CR_2, the changes are similar to those in Lead I.

Fig. 2 shows five tracings from five different patients. The first tracing, A, is Lead I, taken from a patient who suffered from coronary sclerosis; the T waves were inverted in all leads. The T wave in this tracing (Fig. 2) becomes positive in the first beat after the ventricular extrasystole. The same alteration may be seen in the second tracing, B, which is from a 54-year-old patient with coronary sclerosis; Lead II is reproduced. In this case the extrasystoles appear so late that the postextrasystolic pause is no longer than the normal pause. In the third tracing (Fig. 2, C), Lead III is reproduced; there were no T waves in any lead. An inverted T wave appears, however, immediately after a ventricular extrasystole. The first ventricular complex of this tracing also follows an extrasystole, and has, therefore, an inverted T wave. The fourth tracing, D, shows inverted T waves in the chest lead (CR_2) of a 63-year-old patient with coronary sclerosis; the T wave of the first postextrasystolic normal beat becomes positive. The fifth tracing, E (CR_2), from a 52-year-old patient with coronary sclerosis, shows deep, negative T waves. After an auricular extrasystole whose P wave is buried in the preceding T wave, the T wave of the first postextrasystolic sinus beat is less negative, and is followed by a positive component. The first complex of this tracing shows the same thing because it succeeded an auricular extrasystole.

Similar alterations were observed in other cases. Positive T waves were higher or lower in the first postextrasystolic beat, and inverted T waves more, or sometimes less, inverted; positive T waves became negative, and vice versa. Sometimes the changes were found in all leads, in other cases in only two. Occasionally they were visible only in the chest lead. At times, an inverted T wave in Lead I became positive, whereas a positive T_2 became negative. No changes in the QRS complex of the first postextrasystolic beat were observed. Both auricular and ventricular extrasystoles were present in some cases. The T-wave changes were identical after both types of extrasystoles.

Even when definite electrocardiographic patterns existed, the type of change in the T wave of the first postextrasystolic beat could not be predicted. In 19 cases of hypertension, the pattern of left ventricular strain was found; in 9 of these cases the S-T segment of the first postextrasystolic beat was less depressed and the T waves became positive. In 4 instances, however, the negative T wave in Lead I became more negative, whereas, in 6, there were no changes in the T wave in this

lead. The T waves of the chest lead also showed different changes in individual cases. In 9 cases in which there were definite evidence of myocardial involvement and a low or inverted T wave in Lead I, this became either higher or positive after the extrasystoles. In 5 cases in which the electrocardiogram was normal, the positive T wave in Lead I became inverted after an extrasystole. These five patients had cardiovascular disease (hypertension, angina pectoris, coronary sclerosis).
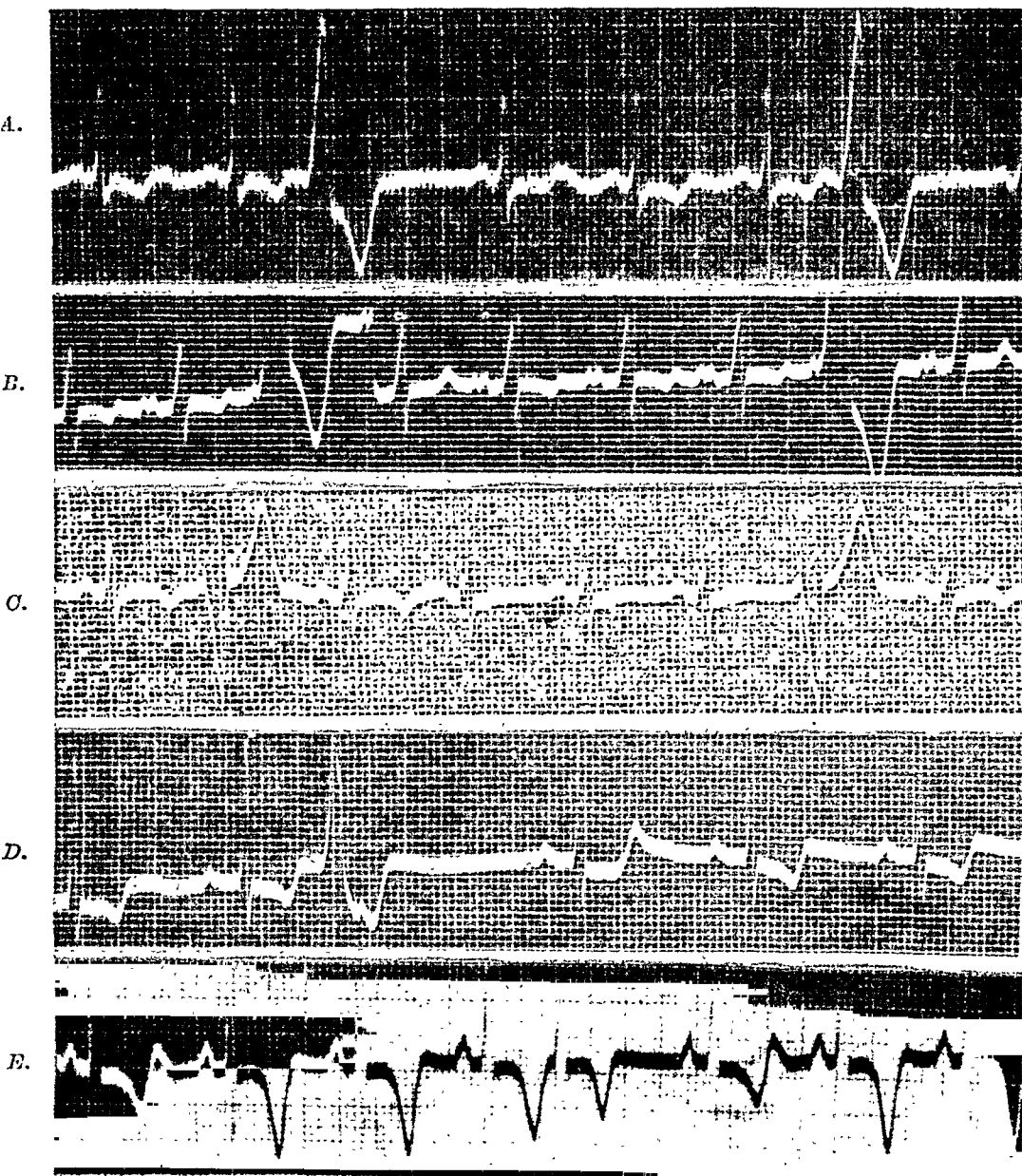

Fig. 2.—Changes in the T waves of the postextrasystolic beats in five cases.

Reference was made earlier to 16 cases in which the electrocardiogram showed no signs of myocardial damage. Other observations indicated, however, the presence of organic heart disease in 9 of these cases. Therefore, there were only 7 patients without definite proof of an organic heart lesion. Since some were over 50 years of age, coronary

sclerosis was possibly present. In 4 of the 7 cases, the T wave became higher after an extrasystole. In the remaining 3 it became lower or inverted. One of these patients (Case 17 of Table I), a 60-year-old man, had a thyroid adenoma; in the other 2 (Cases 18 and 31), who were 60 and 52 years old, respectively, no proof of organic heart disease was found. The patients, however, were not observed sufficiently long to exclude an organic heart disease such as coronary sclerosis. Accordingly, in only three of 57 cases did the electrocardiogram of the first beat after the extrasystole show an alteration of the T wave in the sense of a myocardial lesion (lowering or inversion of the T wave) when there was no decisive evidence for the existence of heart disease.
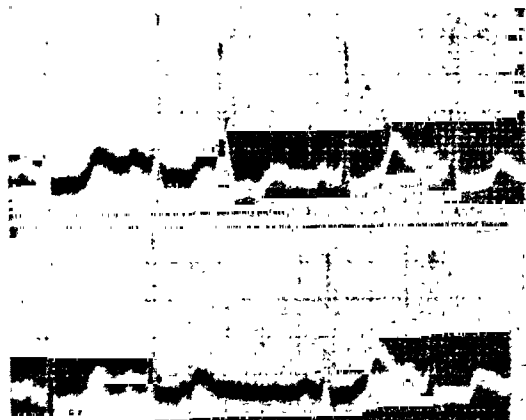

Fig. 3.—The upper tracing shows changes in the postextrasystolic T wave after a conducted auricular extrasystole; the lower shows the same changes after a blocked auricular extrasystole.

These observations seem to warrant the conclusion that the T-wave changes in the first postextrasystolic beat are not rare. A normal or abnormal T wave may become more positive or more negative. Up to the present no definite rules could be drawn which were reliable for all types of changes. It can be said, however, that a change in the T wave in Leads I and II in the direction of negativity, and indicative of an abnormal electrocardiogram, is very rare when the heart is healthy, presuming that it occurs at all.

The changes in the T wave of the first postextrasystolic beat might be ascribed to the extrasystole or to the long pause which follows it.

Tracings like those in Fig. 3 show that the long diastole which follows an extrasystole, and not the extra contraction itself, may cause changes in the final deflection of the first postextrasystolic beat. Auricular extrasystoles, many of which were blocked, and sinus tachycardia with 100 beats per minute were present in this case. The S-T segment was depressed and the T waves were positive. In the upper tracing, two normal beats are followed by an extrasystole. Its origin cannot be ascertained with certainty from this tracing. Since the postextrasystolic pause is not compensatory, and many other tracings from this patient

in other leads showed only auricular extrasystoles, an aberrant auricular extrasystole may be assumed also in this tracing. The normal beat after the extrasystole has a much higher T wave. In the lower tracing, from the same patient, one sees a blocked auricular extrasystole. The normal beat which follows shows the same changes as the postextrasystolic beat in the upper tracing, in spite of the fact that there was no premature ventricular contraction. In another case, both conducted and blocked auricular extrasystoles were followed by the same lowering of the T waves of the first postextrasystolic beat.
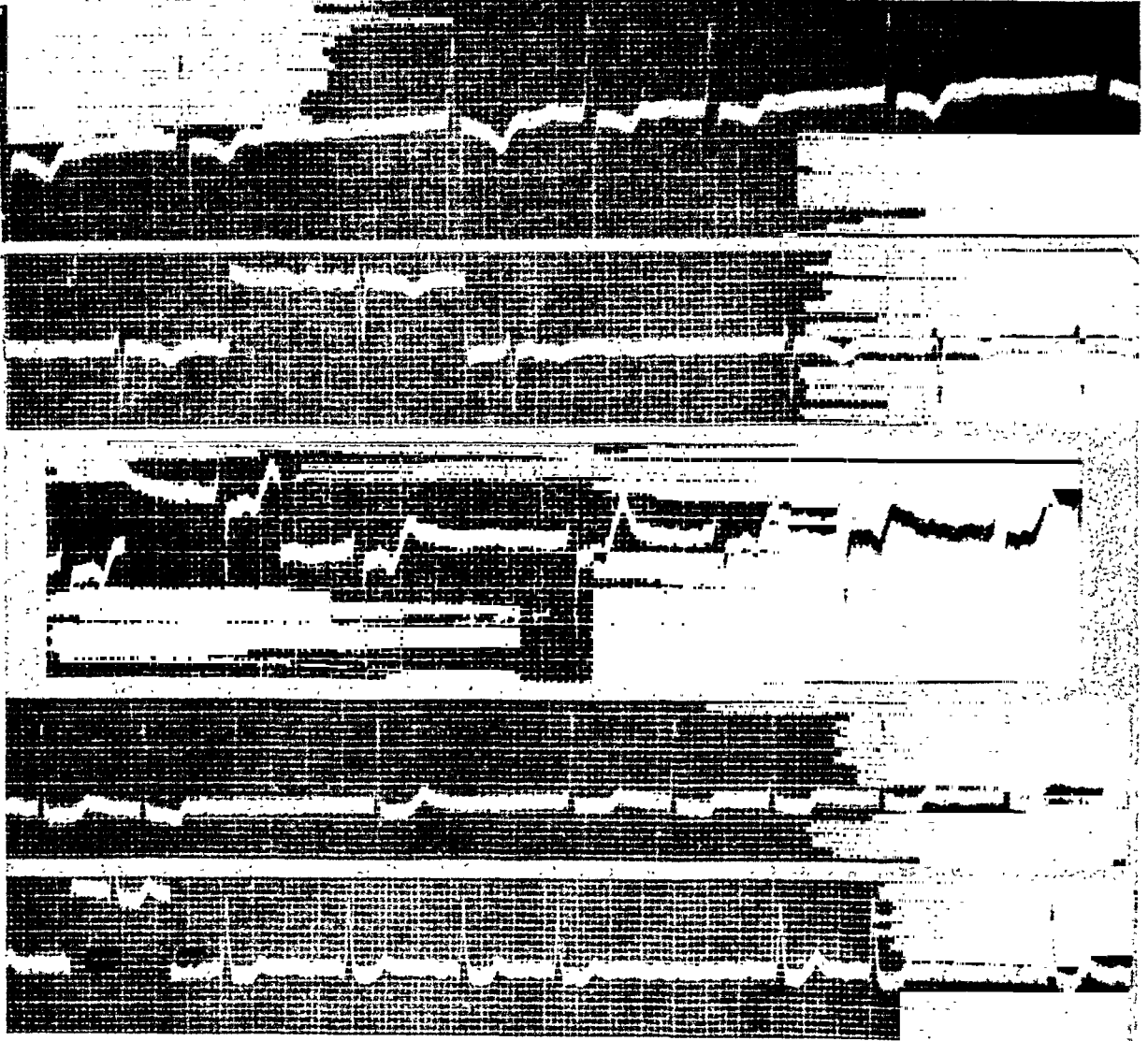

Fig. 4.—Five tracings from patients with auricular fibrillation; the form of the T wave changes with the length of the preceding diastole.

Likewise, it became clear from observations on other arrhythmias that a premature ventricular contraction is not a prerequisite for the changes in the T wave.

In Fig. 4, tracings are reproduced which were taken from five patients who suffered from coronary sclerosis and auricular fibrillation. The first tracing (Lead III) shows clearly that the T waves become in-

creasingly negative as the preceding pause lengthens. The same changes are visible in the second tracing (Lead CR₂). In the third tracing (Lead CR₂), however, the T waves are higher after a longer diastole, and the same situation appears in the fourth and fifth tracings (Lead I). No change in the QRS complex accompanies these alterations of the T waves. In the three-year period during which the tracings were examined in regard to the postextrasystolic T-wave changes, variform T waves, as in Fig. 4, were noted in 22 cases of auricular fibrillation. Since auricular fibrillation was observed in several hundred cases, this phenomenon may be considered uncommon, but by no means rare. In only 5 of these 22 cases was there lowering or inversion of the T waves after a longer pause. In 17 instances they became higher when the preceding diastoles were longer. The type of change varied in different leads from the same patient. Sometimes, after a longer pause, the T wave in Lead I became higher, whereas, in Lead III, it became lower. Occasionally, variations appeared in only one of the limb leads or only in the chest lead. Changes in the T waves in all 22 cases were more pronounced as the length of the preceding diastole increased.
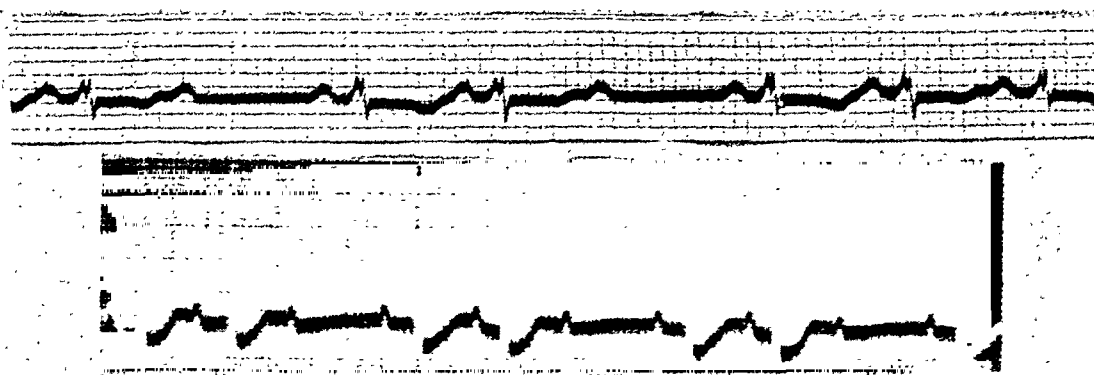

Fig. 5.—Changes in the form of the S-T segment and T wave in two cases of partial heart block after diastoles of different length.

Fig. 5 shows two tracings from patients with disturbances of auriculoventricular conduction and blocked auricular beats, causing the periodic appearance of longer pauses. The T wave of the systole after a longer pause is altered in both tracings. In the upper tracing (Lead I), partial auriculoventricular block (3:2 and 4:3) existed with a constant P-R interval. The T wave of the ventricular complex which follows a longer pause due to the blocking of an auricular stimulus is always deeper than the other T waves. Continuous 3:2 block, with fixed length of the P-R interval, is present in the second tracing. Here again, the S-T segment of the beat after the longer pause always differed from that of the other beats in that it had a much straighter course.

The tracings presented thus far show changes in the S-T segments and T waves alone. If alterations also appear in the QRS complexes, another mechanism should be considered. Fig. 6 shows distinct changes in the QRS complex and in the final deflections of the beats which

Fig. 6.—A case of ventricular extrasystoles and varying intraventricular block.

follow the first two extrasystoles. One sees, however, the same deviations before the third extrasystole and also in the second beat following it. The same changes appeared in other tracings from the same patient, at times without extrasystoles. We may, therefore, assume that the changed form of the postextrasystolic beat in this case was due to an intraventricular disturbance of conductivity.

<div align="center">DISCUSSION</div>

Changes in the T waves after extrasystoles have been noted before. They are frequently to be found in experimental or clinical tracings in textbooks or articles, without remarks by the authors.

To the best of our knowledge, White was the first to notice changes in the postextrasystolic T waves. He described them in a paper on the alternating pulse as "slight alternation of the T-deflection" after premature beats. All of his patients had organic heart disease; tracings obtained from two patients were reproduced. They show deep inversion of the T wave for one beat after the extrasystole.

Bacq described the same phenomenon as "periodic change of the T wave" in hypertensives. In one case the positive T wave became negative after an extrasystole. A similar case was reported by Laubry and Poumailloux as an example of "electric alternans." This patient also had hypertension. The positive T wave was inverted after the extrasystole, the next T was again positive, the following one was negative, and then the T waves remained positive. No attempt is made by these authors to explain the changes in the postextrasystolic T waves.

Von Kapff reported one case in 1930 and 7 more in 1932. Evidence of organic heart disease was available in 6 out of these 7 cases. Among 8 cases published by von Fernbach, 6 patients had signs of heart disease and 7 had cardiac symptoms. T-wave alterations after extrasystoles have also been described experimentally.[2, 12] The T-wave changes in other arrhythmias do not seem to have received attention before.

In order to explain these changes, the following possibilities are worth consideration.

1. *The Altered Form of the T Wave of the First Postextrasystolic Beat is Due to a Change in Intraventricular Conduction.*—A disturbance of intraventricular conductivity may appear or become more pronounced if the diastole is too short and the recovery from the preceding systole is insufficient; this may happen with extrasystoles because the specific tissue conducts twice within a short time, and the postextrasystolic pause may be inadequate to permit full recovery. On the other hand, an intraventricular disturbance of conductivity may be diminished if a beat follows a longer diastole, which permits better recovery. It is known experimentally and clinically that intraventricular conduction disturbances may cause marked changes in the T waves.[14] However, it is the rule that, in such cases, some change in the form of the QRS complex appears (Fig. 6), even if this change consists

merely in the height of a single wave. Since in all the cases collected in this paper there were marked alterations in the final deflection without any change in the initial complex, one cannot attribute the phenomenon to abnormal intraventricular conduction of the first post-extrasystolic beat.

2. *The Abnormality in the Size and Shape of the Heart Due to the Increased Filling in the Long Postextrasystolic Diastole Is the Cause of the T-Wave Changes.*—The augmented filling of the ventricles after an extrasystole, which is clearly visible under the fluoroscope and in the kymograph, causes enlargement of the heart, thereby increasing its area of contact with neighboring tissues of good conductivity. The extent of this contact influences the electrocardiogram markedly. For currents of injury it has been established that prevention of direct contact between an injured area and the diaphragm abolishes the admixture of these currents to the electrocardiogram in the limb leads, and that the high take-off in the electrocardiogram reappears as soon as this contact is re-established.[8, 12] Changes in the T waves of normal persons which depend upon change in posture have also been explained as the result of a difference in the contacts between the heart and the neighboring muscle mass.[13, 15] Since, however, the T wave is registered during the height of the ventricular contraction, it may be assumed that the size and position of the heart at this period are the same for all beats, irrespective of the size of the organ during diastole, providing the heart is normal and empties completely. Under abnormal conditions an incomplete systolic emptying of the heart is possible if cardiac filling in the postextrasystolic diastole is increased. Since the changes in the T waves described earlier usually appear when the heart is abnormal, this possibility cannot be completely discarded.

3. *The Changes in the T Wave Appear in Connection With an Alteration in the Force of the Systolic Contraction of the First Postextrasystolic Beat Caused by the Extrasystole.*—The postextrasystolic contraction is stronger for two reasons: (a) the greater filling of the heart in the long postextrasystolic pause (discussed under heading 5); (b) the "strengthening" effect of the extra contraction on the following beat. Any single contraction which follows another after a short interval increases the height of the next systole.[11, 18] This strengthening effect becomes greater, as the interval between the two contractions becomes shorter. Woodworth has studied this effect on the perfused apex or base of the dog's ventricle. It was confirmed by Rihl on the perfused heart, in situ, under more natural conditions. This phenomenon depends solely on the prematurity of the preceding beat; it may be found even if the postextrasystolic pause is equal to a normal period. It is not always present in experiments on the intact animal because other factors, like changes in ventricular filling, may interfere. Observations, similar to those in Figs. 3, 4, and 5, show, however, that changes in the length of diastole, but not premature contractions, are prerequisites for the alterations in the T waves.

4. *The T-Wave Changes After Extrasystoles Might be Attributed to an Alteration in the Cardiac Blood Supply or Nutrition Caused by the Extrasystole.*[4],[7]—Alteration in the blood supply, or "nutrition," as a consequence of the extrasystoles would not become manifest so quickly nor would it be limited to a single beat. The fact that the same changes in the T wave appeared also in arrhythmias without extrasystoles, moreover, militates against these explanations.

5. *The Changes in the T Waves are Connected With a Change in the Filling of the Heart.*—This possibility was discussed, but discarded, by Kapff. Variations in filling must be assumed to exist in all conditions in which the changes in the T waves described in this paper appear. The stroke volume of the postextrasystolic beat is increased approximately by the amount of blood not moved by the extrasystole, that is, occasionally by as much as 100 per cent. The stroke volume may also be doubled in heart block. Increased filling causes a stronger systole. Whether this, in turn, changes the T wave is a disputed question. According to Pardee, the form of the T wave seems to be influenced by the strength of the contraction; the T wave is larger in athletes and smaller after acute diseases. The different metabolic processes accompanying alteration of contractility seem to be the most probable explanation for the changes in the T waves as described. It is conceivable that changes in the strength of systole are unaccompanied by changes in the form of the T wave under normal conditions, but appear if the heart is in some way "damaged."

Although definite proof for any of these explanations is lacking, those mentioned under headings *1*, *3*, and *4* seem rather improbable. The observations described in this paper show that the postextrasystolic changes in the T waves do not depend on the preceding premature ventricular systole; they appear in connection with the preceding longer pause.

Tracings similar to the second in Fig. 2, in which marked T-wave changes appeared even when the postextrasystolic pause was not longer than the other diastoles, speak against the importance of the length of the pause alone, without changes in the filling of the heart.

Any change in the T wave of the first postextrasystolic beat in the direction of abnormality (lowering or inversion of the T waves in Leads I and II) seems to speak in favor of existing heart disease, because such changes were found only three times in patients without organic heart disease, whereas the number of cases in which no changes in the T waves appear after extrasystoles or during auricular fibrillation is very large.

Almost every third patient reported in this study showed some change in the T wave of the postextrasystolic beat. This is certainly due to the fact that the number of patients with extrasystoles and a normal heart was small in the hospital material. It is noteworthy that, as far as we know, in cases with a marked respiratory arrhythmia, in which, sometimes, very pronounced changes in the length of the diastole

appear, T-wave changes have not been described as yet. Such hearts are usually healthy or not profoundly damaged. Moreover, these changes were not seen in many hundred cases of partial heart block observed personally; the two tracings in Fig. 5 were a rare exception.

From the fact that marked changes in the T waves appear in some arrhythmias, depending exclusively on the length of the diastole, we may infer that, in some cases without arrhythmias, a change in the rate alone, without any intrinsic change in the heart, may cause alterations in the form of the T waves.

CONCLUSIONS

Alterations in the form of the T waves of the first postextrasystolic beat are described and analyzed. These changes are not rare. They are also found after blocked auricular extrasystoles and after long diastoles in auricular fibrillation and heart block.

Lowering or inversion of the T waves in Leads I and II after a long diastole seems to indicate the presence of myocardial damage. Changes in the form of the T waves in cases of myocardial damage may be due to a change in rate only.

The mechanism leading to these alterations in the T waves has been analyzed; they seem to be chiefly connected with changes in the filling of the heart.

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MORPHOLOGIC STUDY OF THE CARDIAC CONDUCTION SYSTEM

PART III: BUNDLE BRANCH BLOCK

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THE bundle branch block concept appears to have originated in the mind of Rothberger. In 1909, he and Eppinger[1] were investigating the effect upon the electrocardiogram of local injury to the myocardium of the dog. They injected a silver nitrate solution into various localities of the heart wall and observed that, occasionally, even minute quantities produced immediate alteration in the ventricular curves and marked physiologic changes in the injured ventricle. When such changes took place, Rothberger suspected that the solution had entered one of the main branches of the His bundle and had produced bundle branch block.

Since two of us[2] have recently reported our inability to find a special muscular conducting bundle in either man or dog, we determined to analyze the information which has accumulated since the early observations of Rothberger and Eppinger. Our purpose was to learn whether the available evidence justifies the belief that the so-called bundle branch block complexes, obtained from experimental animals and man, are really due to blocking lesions in the branches of a special conducting system. In this communication, we present our analysis and our conclusions.

Eppinger and Rothberger[3] (1910) planned experiments to verify the theory which developed from their previous observations. With specially constructed knives, they entered the cavities of both lower chambers of the canine heart and made transverse sections into the upper part of the interventricular septum on the right and left sides (Fig. 1, A), and considered that their incisions were successful when they were followed immediately by the broad ventricular complexes shown in Fig. 1, B and by a "nachhinken" (limping after) of the injured ventricle. When these two changes occurred, they believed that the right or the left branch of the His bundle had been completely severed. However, they did not state how they were able to recognize the branches, nor how they could microscopically distinguish the branches from the neighboring muscle elements. They offered no control observations to exclude the possibility that the electrocardiographic
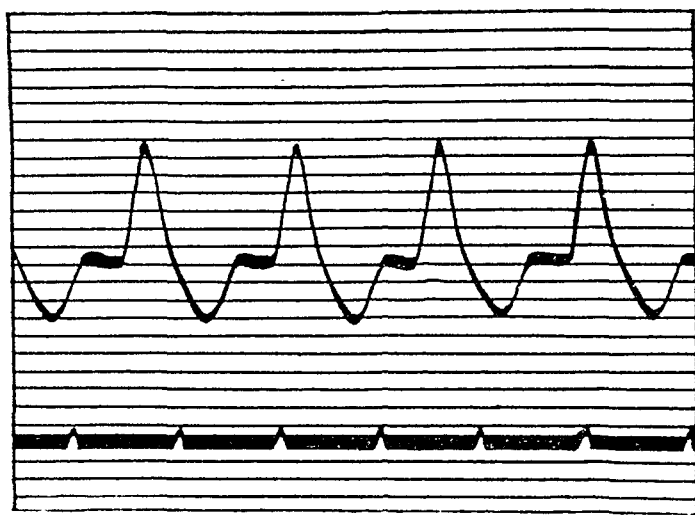
and structural changes were the result of experimental mutilation or of the severing of adjacent muscle fasciculi.

Independent of the Viennese investigators, Barker and Hirschfelder[4] had, in 1909, published their results after severing the left bundle branch, but they concluded that the muscle bundles described by Tawara had no special function.
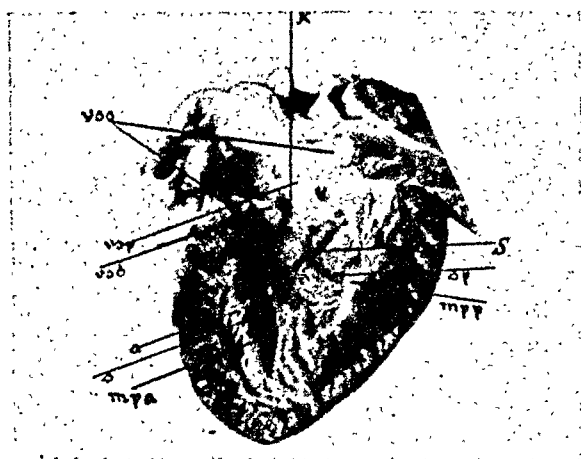
A.

Fig. 1.

B.

Fig. 1.—The first experiment on bundle branch block.   (Eppinger and Rothberger.) A, Incision of left septum.   B, Resulting electrocardiogram—anoesophageal lead.

Rothberger and Winterberg[5] continued the experimental observations on bundle branch block in the dog, while Eppinger and Stoerck[6] searched for cases of bundle branch block in man, for by this time Einthoven's string galvanometer had been introduced into the clinic. Here, however, the three limb leads were employed, whereas Rothberger continued to rely on the anoesophageal lead.   Since Lead III is somewhat analogous to the experimental anoesophageal lead, the clinical observers sought the diphasic, widened QRS complex in Lead III, and

considered that the form of the complex in Lead III determined not only the presence or absence of bundle branch block, but also the location of the blocking lesion.

When the right bundle branch was cut, Eppinger and Rothberger had obtained a ventricular complex like that of a left ventricular extrasystole. When, therefore, Eppinger and Stoerck found widened complexes in which the main spike was inverted in Lead III, they suspected that the right bundle branch had been blocked, and, when the main deflection was upright in the same lead, that the left had been interrupted. In two cases in which the complexes of right bundle branch block were traced (Fig. 2), necropsy was performed. In both, serial sections showed that the right branch was completely interrupted by fibrosis.
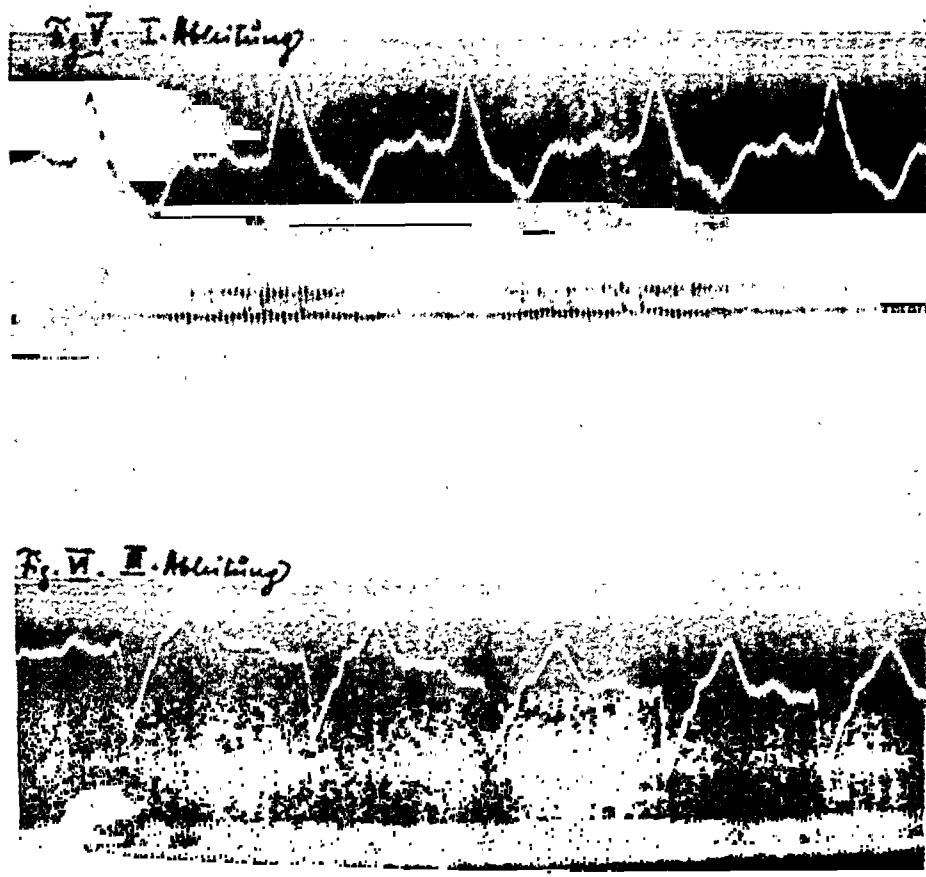

Fig. 2.—Right bundle branch block. (Eppinger and Stoerck.)

whereas the left branch was normal. The authors did not state how they distinguished the bundle branches from the ordinary myocardium. In their cases of right bundle branch block, Eppinger and Stoerck found the main ventricular deflection in Lead I directed oppositely to the main spike in Lead III.

This difference between the direction of the complexes in clinical and experimental bundle branch block disturbed Rothberger, who by this time was using Lead I as well as the anoesophageal lead in his experimental work on the dog. He and Winterberg found, after sectioning one branch, that the main initial ventricular deflections had the same direction in both leads. Consequently, they suspected that the block was not complete in the cases reported by Eppinger and Stoerck. They, therefore, undertook to produce partial block by cutting the posterior limb, the anterior limb, and the apical twigs of the left branch, and also the twigs from the right branch—individually and in various combinations. By these procedures, they were able to modify the ventricular complexes. Since the observations of Rothberger and Winterberg are startling, we give them in some detail.

1. The authors present a detailed, gross description of the main right and left branches of the His bundle, including their secondary branches. The illustrations, "drawings from nature," clearly show the posterior and anterior subdivisions, as well as the apical twigs of the left bundle branch; they show twigs given off from the right branch in the neighborhood of the septal papillary muscle; they do not show the junction of the branches and the stem.

2. They agree with Tawara that the bundle and its branches constitute a closed system.

3. They report:

   a. When only the anterior limb of the left branch was severed, no constant changes occurred. When only the posterior limb was cut, the R became taller and the S more shallow in the anoesophageal lead.

   b. When the left branch was intact, severing the right branch usually produced a left-sided extrasystole.

   c. The lengthening of the QRS interval, which always followed complete sectioning of the left branch, was not always noted after complete sectioning of the right.

   d. When the right branch was sectioned after *almost* complete severing of the left, complete A-V dissociation did not occur. (In one experiment complete heart block occurred after a cut limited to the posterior limb.)

   e. When the left branch was severed, the complexes of left bundle branch block were obtained, even though the right branch had previously been cut.

   f. Marked changes in the ventricular curves were often observed when the bundle branches were intact.

   g. Complete experimental right or left bundle branch block produced initial main deflections similarly directed in Lead I and in the anoesophageal lead.

Rothberger and Winterberg do not state how they distinguished conducting tissue from that of the ordinary myocardium. They surmised

that, in the dog, as in man, not all of the pseudotendons contained Purkinje elements. They do not describe or show by illustration the junction of what they call the branches of the His bundle and the main stem. Nor do they account satisfactorily for the convenient appearance of a "tertiary center" after severing the left branch in animals whose right branch had already been sectioned.

While these studies were in progress in continental Europe, Lewis[7] and his associates in London were investigating experimental and clinical bundle branch block. Using dogs and one monkey, Lewis repeated the branch sectioning experiments of Rothberger and his associates. He found, like Rothberger and Winterberg, that, in most dogs when the right or left branch was cut, the initial ventricular complexes had the *same direction in all leads*. To such deflections, Lewis applied the term *concordant*. However, in some dogs and in the monkey, the initial deflections pointed oppositely to one another in Leads I and III. Such curves he called *discordant*. Lewis thought that discordant curves were caused by the paucity of pseudotendons in the hearts which traced them. In 1915, Lewis presented to the Royal Society the observations which he and Rothschild[8] had made on the spread of the excitation wave in the mammalian heart. Because of masterly diction and clear illustrations, these lectures made a deep impression on physiologists and cardiologists (Fig. 3).

From their observations, Lewis and Rothschild concluded that the cardiac impulse travels through the His bundle approximately at the rate of 3,000 to 4,000 mm. per second, through the Purkinje network at the rate of 1,500 to 2,000 mm. per second, and through the myocardium at the more leisurely rate of 300 to 500 mm. per second. They explained the activation of the blocked ventricle as follows: the wave of excitation passes from the septal endocardium of the uninjured ventricle, through the septum, into the Purkinje network of the blocked ventricle, and thence into the ordinary myocardium. Only the eminence of Lewis and his masterly presentation can explain the general acceptance of this amazing theory.

We attempted, in vain, to bring to view a special conducting system in two canine hearts, according to the direction of Lewis and Rothschild; Barker, Macleod, and Alexander's[9] observations on the spread of the wave of excitation in mammals do not fully corroborate the findings of Lewis and Rothschild; Robb, et al.,[10, 11] found that the speed of the electrical impulse through the ventricular muscle was $2,375 \pm 128$ mm. per second, and also showed that Lewis, when he thought he had cut muscle bands crosswise, had actually made his cut parallel to the fibers. It is, therefore, apparent that there is need for a reinvestigation of the mode of activation of the mammalian ventricles.

While Lewis' experimental work was in progress, Carter[12] was searching the records of the London hospitals for electrocardiograms indicating bundle branch block. In 1914, he published a clinical study of

A.

B.

Fig. 3.—Drawings of canine ventricular conduction system, after staining with Best's alkaline carmine. (Lewis and Rothschild.) A, Right; B, Left.

twenty cases of right, and two cases of left, complete bundle branch block. The criteria he employed for the selection of his cases were the following:

1. Presence of P summits.
2. P-R interval frequently beyond 0.2 second.
3. QRS interval exceeds 0.1 second, and, as a rule, constitutes more than one-third of the entire ventricular complex.
4. Increased amplitude of initial deflection.
5. T, usually in the direction opposite to that of the prominent initial deflection, may be upright or inverted.
6. Initial deflection almost always shows notching in at least one lead; many bizarre forms seen.
7. T frequently much exaggerated.

The only evidence presented by Carter for the validity of his criteria was the microscopic observations in the two cases of Eppinger and Stoerck. However, the complexes in those cases do not show increased amplitude. It is not clear to us what other grounds Carter may have had for choosing his criteria, but it is apparent that he selected only cases in which there were curves that simulated preponderance deflections to represent complete right or left bundle branch block.

In the year that Carter published his clinical observations on bundle branch block, Cohn and Lewis[13] reported their pathologic study of four cases of bundle branch block (from serial sections). In one case, Cohn had difficulty tracing the right and left branches, but found a large amount of connective tissue involving the left branch. In another case, he found no lesion in the branches. In the third case, the stem and the branches were normal. In the fourth case, there were a slight increase of connective tissue in the stem and atrophy of fibrils in the left branch. Cohn and Lewis, therefore, concluded "that the cardiac conduction problem cannot be solved in the domain of pathologic anatomy."

From London, the interest in bundle branch block spread to the United States. Oppenheimer and Rothschild,[14] in 1917, published a study of sixty-two cases of intraventricular conduction defects. These cases clearly showed what a small percentage (6.4) of such defects actually fulfill Carter's criteria. Twenty-five of their patients had died; fourteen had come to necropsy. In eleven cases, microscopic serial sections were made, and, in eight of these, there was coronary arterial occlusion; in four, marked nodular sclerosis of the coronary arteries; and, in thirteen, marked patchy fibrosis of the myocardium, especially prominent in the endocardium and subendocardium of the left ventricle. From their observations, Oppenheimer and Rothschild concluded that atypical bundle branch block complexes were due to lesions involving the main branches of the His bundle, the twigs, and the Purkinje plexuses, and, therefore, named them *arborization block*. They stated that such complexes carried a poor prognosis.

The arborization block theory of Oppenheimer and Rothschild was accepted by some observers and rejected by others. For example, Carter[15] (1918) reported a clinical study of thirteen cases of arborization block, with a histopathologic study of one; and Willius[16] (1919) reported a clinical study of 138 cases of arborization block and also found that arborization block carried a poor prognosis. But Smith[17] doubted the arborization block explanation. From his own experiments with bundle branch block, he made the startling observation that severing a bundle branch was not in itself sufficient to produce a bundle branch block complex, and that such a complex was traced only after the injured ventricle had become dilated. Hence, Smith concluded that two factors, severing the branch and fatigue, were necessary for the production of the bundle branch block complex. Wilson and Herrmann[18, 19] (1920, 1921), in an analytical review and an experimental study of bundle branch block, concluded that the evidence presented by Oppenheimer and Rothschild did not sustain the arborization block theory.

Wilson and Herrmann were able, first, to construct complexes which varied from the normal biocardiogram to that of complete bundle branch block by combining Lewis' theoretical dextro- and levocardiograms at varying intervals; second, to produce complexes varying between normal and complete bundle branch block by making the usual incision into the right upper portion of the septum, and eliciting right extra-systoles by electrical shock at varying intervals; third, to produce the same variation in complexes by compressing the right septum and permitting the septal myocardium to recover. From these observations, Wilson and Herrmann concluded that the complexes which fulfill Carter's criteria represent complete bundle branch block, and that the atypical complexes with prolonged QRS intervals are due to incomplete bundle branch block.

Stenstroem,[20] in a series of communications (1922, 1924, and 1927), supported Wilson and Herrmann's explanation of atypical bundle branch block, and presented evidence showing that electrocardiograms of transient bundle branch block and of varying forms of bundle branch block were the result of incomplete bundle branch block.

While the cited observations were being made, other studies had been published which threw doubt on the entire orthodox bundle branch block concept. Boden and Neukirch,[21] working with transfused human and animal hearts, cut away the right ventricle and found that the resulting electrocardiogram had the main initial spike downwardly directed; on removal of the left ventricle, the electrocardiogram traced by the right ventricle had its main deflection upwardly directed. They also rotated the heart on its longitudinal and anteroposterior axes, and discovered that the heart's position profoundly affected the form and direction of the ventricular complex. Some years later, Meek and Wilson[22] fully corroborated Boden and Neukirch's observations con-

cerning the effect of cardiac position on the ventricular curves of the electrocardiogram. In 1920, Fahr[23] published an analysis of the human electrocardiogram from which it may be inferred that he questioned Lewis' conception of the levo- and dextrocardiogram. Fahr concluded that Lewis' statement concerning the rotation of the electrical axis in bundle branch block was also probably erroneous, and that the common type of bundle branch block was left, and the less common, right. In spite of these startling reports, the older concepts prevailed. Willius[24] (1929), in his *Clinical Electrocardiograms*, classified bundle branch block complexes as follows:

I. Complete bundle branch block—the complexes which fulfill Carter's criteria.
   a. Right bundle branch block—the common type.
   b. Left bundle branch block—the less common type.
II. Incomplete bundle branch block—the atypical ventricular complexes with a QRS interval of 0.1 second or more.

The same year (1929), a patient with purulent pericarditis entered the University Hospital at Ann Arbor, Michigan. He was operated upon, and the wound, which remained open, exposed the anterior surfaces of the right and left ventricles. The alert workers at the Heart Station of the hospital seized the opportunity to make electrocardiographic studies of the exposed heart. In a series of well-planned and well-executed experiments, they ascertained, first, the spread of the wave of excitation over the anterior surface of the heart; and, second, the form of the extrasystoles originating at the various points on the surface of the two ventricles. They used the technique of Lewis and Rothschild, and employed points analogous to theirs, from which they ascertained the time of arrival of the wave. The readings obtained by Lewis and Rothschild from points on the ventricular surface of the dog heart are consistent with Lewis' theory of the spread of excitation in the ventricles, in that they show that the earliest point of arrival of the wave is on the anterior surface of the right ventricle just over the papillary muscle, and that it arrives later over the conus arteriosus and at points near the atrioventricular groove in the right and left ventricles.

The readings obtained by Barker, Macleod, and Alexander from points *g*, *b*, *a*, and *i* (Fig. 4) show that the earliest point of arrival of the wave of excitation is near the atrioventricular groove on the right ventricle and over the conus arteriosus, and that it arrives at an appreciably later time at the "earliest" point of Lewis.

The Michigan investigators also found that concordant as well as discordant extrasystoles could be produced by stimulating both the right and left ventricles, and that, in Lead I, all of the chief initial deflections from the right ventricle are upward, and all from the left ventricle, downward; in Lead III the ectopic beats produced by stimulating the conus and the area adjacent to it in the left ventricle are up-

wardly directed, whereas those from the other exposed regions of the heart point downward.

The factual observations made by Barker, Macleod, and Alexander[9] were soon verified by other investigators, including Marvin and Oughterson[25] and Lundy and Bacon.[26] Kountz, Prinzmetal, Pearson, Koenig, and Smith[27, 28] repeated the experiments of Barker, Macleod, and Alexander on transfused human hearts and on monkey hearts. Their observations, too, support those of the Michigan workers. The St. Louis investigators, making the usual transverse cut into the upper part of the septum of four transfused human hearts, found that, when the cut was made on the left side, the complexes of the common form of bundle branch block were traced, and, when made on the right side, bundle branch block of the less common type developed.
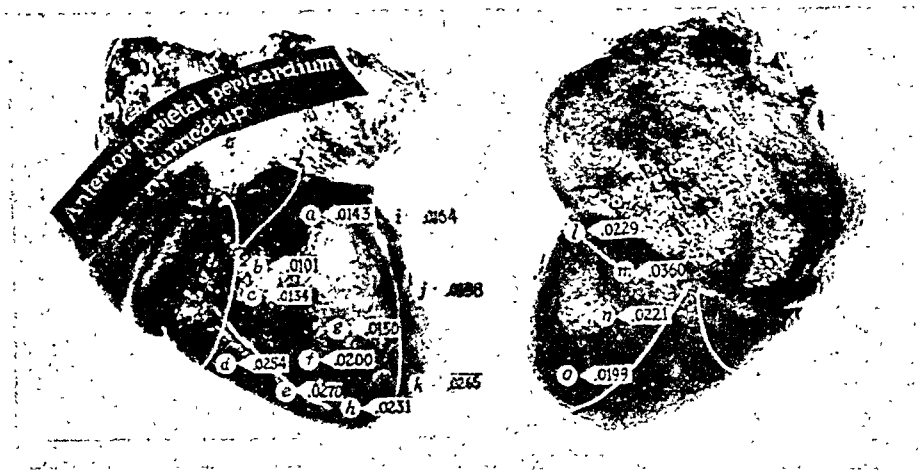

Fig. 4.—Time of arrival of wave of excitation in the human heart. (Barker, Macleod, and Alexander.)

Furthermore, Wilson, Macleod, and Barker,[29] in 1931, carefully re-examined the observations upon which Lewis had based his statement concerning the levo- and dextrocardiogram and the rotation of the electrical axis in bundle branch block, and arrived at the conclucion that the basic data from which Lewis had made his determinations were probably erroneous. By using the second part of the initial ventricular complex instead of the first, as Lewis had done, they showed that the electrical axis swung from right to left in the common form of bundle branch block, so that the movement of the electrical axis was also consistent with the new theoretical site of the lesion in bundle branch block. Fenichel,[30] a year later, published an elaborate and involved analysis of the electrocardiogram, and concluded that the electrical axis rotated in a manner consistent with the European view of bundle branch block. Then, Robb, Easby, and Hiss,[11] in a critical analysis of the methods employed in the determination of the electrical axis, stated that the basic assumptions employed in its determination were not sound.

The meagerness of our own knowledge of the electrophysics of the heart precludes any attempt to evaluate these conflicting observations

and conclusions. Perhaps when cognizance is taken of the form of the distinct muscle bands of which the myocardium is composed, studies like the ones just cited will be more profitable to physiology and medicine.

During this period, evidence had been accumulating from other sorts of experimentation which supported the American view that bundle branch block complexes of the common form were due to disturbances in the left rather than in the right ventricle.

Eppinger and Rothberger had noted in their early experiments concerning bundle branch block that the injured ventricle "limped after" the uninjured; and had been able to demonstrate a slight but detectable delay in the pulse wave coming from the injured ventricle. Other investigators of experimental bundle branch block had verified their observations. Wolferth and Margolies[31] and Braun-Menéndez and Solari[32] were able to demonstrate that in human cases there was a similar lag. Finally, by employing their serial precordial leads, Wilson, Macleod, and Barker[33] were able to show that the wave of excitation appeared late over the left ventricle in the common form of bundle branch block and late over the contralateral ventricle in the rarer form.

Thus, rather clear-cut evidence from various kinds of experimental approach strongly supports the view first expressed by Fahr that the common form of bundle branch block is due to a lesion on the left side of the septum. In spite of this evidence, Katz and Ackerman[34] asserted that it is not safe to make a diagnosis of right- or left-sided bundle branch block from the form of the ventricular complex. They suggested the terms "common" and "less common" instead of left and right bundle branch block, basing their contention on the work of Boden and Neukirch, and of Meek and Wilson, which has already been reviewed, and on their own experiments on the dog, in which they were able to change one type of bundle branch block into the other by extreme rotation of the heart.

Nathanson,[25] Lundy, Treiger, and Davison,[36] and Kountz, Prinzmetal, and Smith[26] also showed that the heart's position in the thorax influenced not only the amplitude, but also the direction of the ventricular complex. Nichol,[27] who repeated the work of Katz and Ackerman, corroborated their findings, but observed that the extreme rotation required for the change from one type of bundle branch block to the other was possible only under experimental conditions. He, therefore, concluded that in human cases of bundle branch block it was safe to designate bundle branch block complexes as either right or left.

The new factual information concerning bundle branch block, secured mostly by American investigators in the last two decades, rendered the older classification of bundle branch block complexes inadequate and obsolete. Further attempts were made, therefore, to classify bundle branch block complexes into more useful and more logical groups. Graybiel and Sprague[28] (1933) found 395 cases of defective

ventricular conduction among 16,000 electrocardiograms. These they arranged into four main groups:

Group I. Left bundle branch block—common type (125 cases).
    a. Homophasic type—in which the initial and final ventricular deflection have the same direction (99 cases).
    b. Heterophasic type—in which the final deflection is directed oppositely to the main spike.

Group II. Right bundle branch block—less common type (29 cases). Heterophasic only.

Group III. Intermediary type (81 cases).
    QRS, slurred; QRS interval more than 0.1 second; T often, but not always, opposite to the main initial deflection. QRS is often similarly directed in Leads I and III. The authors think these represent incomplete block.

Group IV. Slight intraventricular block (160 cases).
    QRS, slurred and notched; QRS interval, normal or slightly prolonged; T, variable. The authors consider this group to represent a transitional or slight block.

Graybiel and Sprague found the prognosis similar in all four groups; the average duration of life was one year and two months after discovery of the abnormal tracings. They concluded that the prognosis was not dependent upon the type of ventricular complex, but upon the general condition of the patient.

By employing serial precordial leads, Wilson, Macleod, and Barker[33] discovered that, in all cases of prolonged QRS interval in which a wide S was present in Lead I, regardless of the depth of the S wave and of the amplitude and direction of the ventricular complexes in the other leads, the wave of excitation appeared late over the right side of the heart. They concluded that bundle branch block complexes with a wide S_1 represent right bundle branch block.

Bayley[39] (1934) critically examined all the available cases in the University Hospital at Ann Arbor, Michigan, in which the QRS interval was 0.12 second or more, and the amplitude at least 0.5 cm. in one lead. He thought such cases represented complete bundle branch block. Of the 173 cases examined, 103 were found to be complete left bundle branch block, and 70, right bundle branch block. Bayley divided the cases of right bundle branch block into four groups:

Group I. With characteristic curves of the less common type of bundle branch block (14 cases).
Group II. Differing from Group I in that the amplitude of the R was greater than that of the S (23 cases).
Group III. With a slender, deep spike in Lead III (28 cases).
Group IV. With R absent in Lead III (5 cases).

Bayley found that no single etiologic factor or any particular kind of heart disease was responsible in any of the four groups.

In 1939, Freund and Sokolov[40] reported an analysis of 210 cases of bundle branch block which they classified into four main groups:

Group I. Common type—left bundle branch block.
    a. Homophasic—Graybiel and Sprague (10 cases).
    b. Heterophasic—Graybiel and Sprague (80 cases).

Group II. Less common type—complete right bundle branch block.
    a. Bayley's Group I (14 cases).
    b. Bayley's Group II (18 cases).
    c. Bayley's Group III (21 cases).
    d. Bayley's Group IV (6 cases).
    e. Wilson, Johnston, and Barker's[41] "rare" type (3 cases).

Group III. Bundle branch block without localization characteristics but with a QRS interval of 0.12 second or more (7 cases).

Group IV. Arborization block—with a QRS interval of 0.1 second or more, notching of R, low voltage in all three leads, and absence of the typical diphasic curve; also, cases with a QRS interval of more than 0.12 second, without distinguishing features (50 cases).

Freund and Sokolov found that left bundle branch block of the homophasic type had the best life expectancy (4.7 years). They also found that Group II (a and b) had the average life expectancy for the entire series, but that the survival period for Group II (e) was almost twice as long as that for any other type of right bundle branch block. In the three cases of the "rare type" of right bundle branch block, the condition of the patient was terminal when the electrocardiogram was taken. The prognosis was the worst for the cases that they called arborization block (0.45 of a year).

Finally, Willius,[42] who has been interested in the clinical phases of bundle branch block for decades, with his collaborators, Reeser and Dry, simplified former classifications and recorded life expectancy according to their grouping.

The Rochester investigators questioned the use of the terms "complete" and "incomplete" as applied to bundle branch block, and, on the basis of Yater's[43] histopathologic study, concluded that the lesions in the common type of block occur on the left side, and those in the less common, on the right side. They arranged their cases into:

    I. Concordant—the classic form, with the T directed oppositely to the main initial spike.
    II. Discordant—the less classic form, with a QRS interval 0.1 second or more, variable amplitude, and the T directed similarly to the main initial deflection in Leads I and III.
    III. Bundle branch block of the wide S-wave pattern.

Of the 1,611 cases studied, 756 were concordant, of which 23 were right bundle branch block, and 733, left; 363 cases were discordant;

492 were of the wide S-wave type. The life expectancy of the thee types is graphically shown in Willius' illustration.

The classifications just listed do not appear to dispel the mist which surrounds the bundle branch block concept. Perhaps there is no logical basis for classifying cardiac disorders according to such electrocardiographic patterns. However, there seems to be agreement among the various classifiers that the empiric criteria of Carter are no longer adequate. Most of his imposing list of essential characteristics have been dropped. The only criterion that remains is a prolonged QRS complex, but, even here, there is no agreement in regard to its length. Wilson's assertion that complete bundle branch block is present when the QRS interval is 0.12 second or more is generally accepted, and the consensus among American investigators is that the common type of bundle branch block complex represents left ventricular lag, and the less common, right. But European investigators do not consider the evidence brought forth in America as decisive. In fact, Rothberger and Goebel[44] state that the evidence presented by Barker, Macleod, and Alexander does not support their conclusion. And, since the whole bundle branch block concept has an anatomic basis, Rothberger rightly holds that the location and extent of the blocking lesion, and that alone, should determine whether the block is right or left, complete or incomplete. Since the orthodox conception of cardiac conduction, as well as the bundle branch block concept, is based upon anatomic assumptions, it follows that the whole bundle branch block concept is dependent upon the existence of a specific anatomic structure, the His-Tawara system, and upon the presence of demonstrable morbid changes in one or the other branch of the His bundle.

Let us, therefore, next consider the evidence for these assumptions. The orthodox concept of cardiac conduction assumes that the myogenic atrioventricular bundle begins in dendrite-like muscle fasciculi lying among atrial muscle fibers. These gather the wave of excitation from the atrial muscle, and shunt it into a compact muscular bundle where the cardiac impulse is held insulated from the rest of the myocardium as it travels from behind the central fibrous body to the level of the septal papillary muscles. Here it bursts with explosive suddenness over the entire subendocardial ventricular musculature, whence it travels radially through the myocardium. The orthodox theory is based on the assumption that the myocardium is a syncytium. We wonder how anyone can look at the myocardium either microscopically or grossly and still retain this conception. To be sure, the branches of individual myocardial muscle cells intermingle with one another, but, from the very time in embryonic life that the muscle fibers are differentiated, the individual cell borders are distinct, and the fasciculi of muscle fibers within the myocardium are surrounded by connective tissue sheaths as distinct as those found in skeletal muscle (Fig. 5). Recently, the gross anatomy of the muscle bands which compose the myocardium of the ventricle has been meticulously described and profusely illustrated in the articles

published by Robb.[6] The separate vascular supply, as well as the origin and insertion of the muscles revealed in the specimens prepared by Robb, needs but to be seen to be appreciated. These muscle bands have been seen for many centuries by the anatomists who have looked for them. They may be seen by anyone who will take the time to remove the visceral pericardium and do a careful dissection. As is clearly shown by the dissections of Robb (Fig. 6), the muscles of the ventricular myocardium have their origin and insertion in the fibrous ring which separates the atria from the ventricles. All the muscles with the exception of the deep bulbospiral are common to both ventricles, so that both ventricles function as one, a fact brought out by Harvey more than three hundred years ago. We have already
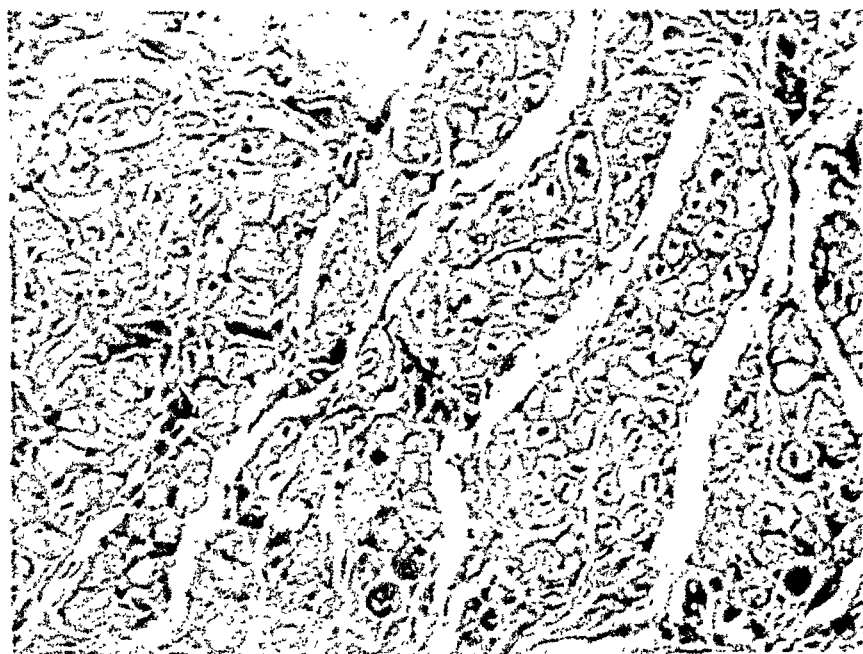
Fig. 5.—Heart muscle fasciculi showing interstitial connective tissue.

shown that large numbers of ganglion cells are located in the atrioventricular groove near the origin of these muscles. Therefore, until it is demonstrated that these muscles are not activated by the nerve elements present at their origin, until it is shown that the wave of excitation does not travel along the muscle bands in the heart muscles as it does in the skeletal muscles, and until it is disproved that the contraction and relaxation of the muscles of the ventricles do not proceed in the same efficient and purposeful manner as is the case in the limb muscles, it seems illogical and unnecessary to assume that the activation of the ventricle should be wholly dependent upon a microscopic muscle fasciculus.

It seems appropriate to sketch briefly the evolution of the anatomic basis of the modern concept of cardiac conduction. When, in 1883, Gaskell[46] noted that the tortoise ventricle continued to beat normally

after zigzag cuts in the adjoining auricular wall, he felt certain that he had destroyed all nerve pathways to the lower chamber, and rejuvenated the myogenic conception of impulse transmission to explain the synchronous contraction of the heart chambers. Around the opening of the atrioventricular valves, he found muscle fibers which were paler and more slender than the rest of the muscle elements, assumed that the paler ones were more embryonic than their fellows, and concluded that impulse conduction was their special function.
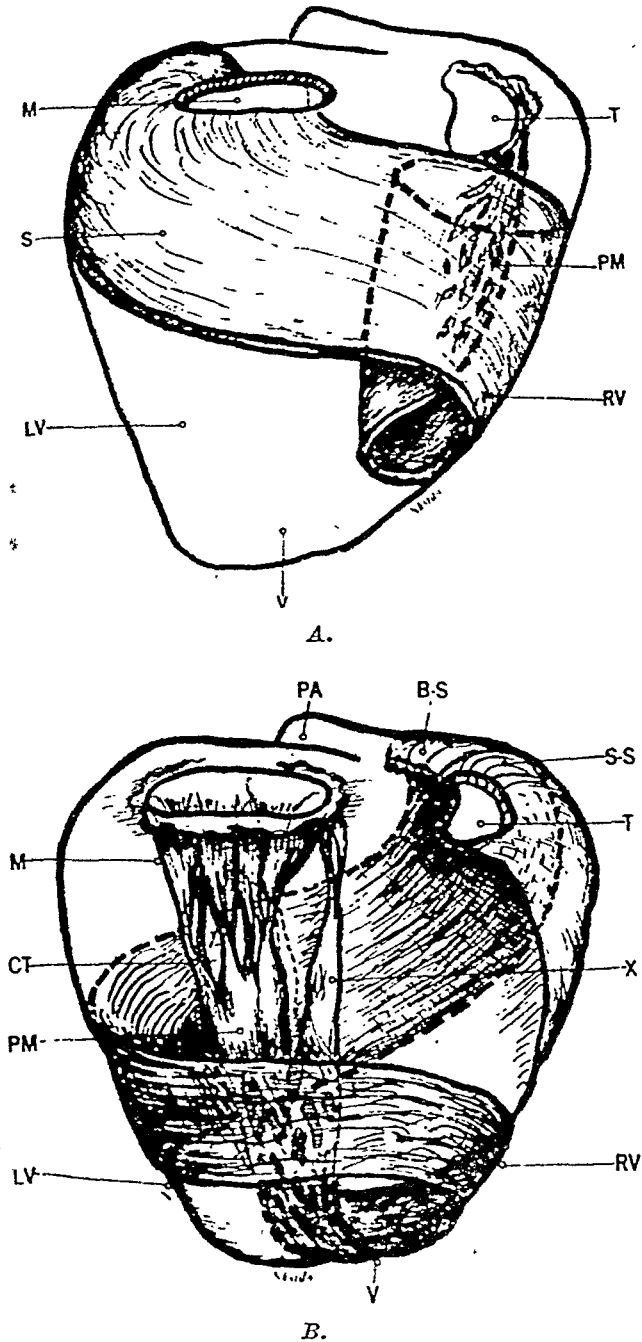
Fig. 6.—A and B. Cardiac muscle bands. (Robb.)

In 1893, Kent[47] reported that he had found in man and other mammals *numerous* muscle bridges between the atria and the ventricles in the atrioventricular groove; in the same year, His, Jr.,[48] stated that, after diligent search, he had discovered in man and other mammals *a* muscle

bundle originating in the atrial septum and extending into the left ventricle. But the illustrations of the bundle which accompany His' communication bear little resemblance to subsequent pictures of the His bundle.

In 1906, Tawara,[49] a Japanese pupil of Aschoff, published his famous monograph on the cardiac conducting system in mammals. Tawara accurately described a part of the Purkinje system in ungulates, and noted that the main trunk and the branches of what we have called the Purkinje bundle were isolated from the rest of the myocardium by a connective tissue covering. Tawara saw *with the naked eye* a similar bundle in man and dog.

In 1906, Keith and Flack[50] reported that they had examined 130 human hearts and stated: "In properly prepared hearts the bundle is *big* enough to be found and dissected out by knife and forceps alone."

In 1913, Tandler,[51] another pupil of Aschoff, described and clearly pictured the His bundle in man. Since that time the His bundle has been seen and its gross appearance described by Moenckeberg,[52] Spalteholz,[53] Yater, et al.,[54] and others.

Similarly, the conducting system of the dog has been described as almost identical with that of man. Before 1925, all experimental investigators of bundle branch block *saw* the branches of the His bundle through the semitransparent endocardium in the dog. Lewis and Rothschild[8] present remarkable drawings of the right and left branches of the His bundle and of the entire Purkinje system in the dog. In the latest edition of his book, Lewis[55] states that the branches of the His bundle *can be seen* through the endocardium of the dog, although he admits that the branches are not distinct. Rothberger and Winterberg's[5] "drawings from nature" show not only the main branches, but also the twigs of the right and left branches in the dog.

In 1931, Mahaim[56] published his monograph on the His-Tawara system. In it occurs the astonishing statement that the His bundle in man is *not* visible to the naked eye, that it can be found and followed only by means of serial sections, and that *every* section of the series must be saved lest a branch or a lesion be lost (Fig. 7).

Thus, it appears that, like a new star, the His bundle could be readily seen for nearly three decades, after which it suddenly shrank to a magnitude not visible to the naked eye! For, from the time of Mahaim's monograph until now, we have not encountered in the literature any claim by experimental or clinical students of the conducting system that they have seen the His bundle or its branches, either in dog or in man, with the naked eye.

Students of the anatomy of the system now stress that it must be located and studied by means of serial sections. Not all of them urge that each section of the series be studied, but they emphasize that great care and almost superhuman skill is required to study the normal His bundle and its histopathology. The descriptions of the histologic structure of the His-Tawara system as given by Tawara, Moenckeberg, Lewis,

Yater, and Mahaim can equally well be labeled descriptions of ordinary myocardial fibers; and the excellent drawing of the histologic structure of the left branch of the His bundle in Cohn and Trendelenburg's[57] article, and the remarkably clear microphotographs of the bundle branches in Mahaim's monograph (Fig. 7) are indistinguishable from those of the neighboring muscle fasciculi. None of the students of the particular muscle fasciculus which is called the His bundle mentions the obvious fact that there are literally hundreds of muscle fasciculi in the ventricular subendocardium which can be followed with relative ease by means of serial sections. Such muscle fasciculi can also be separated from their fellows by careful dissection.
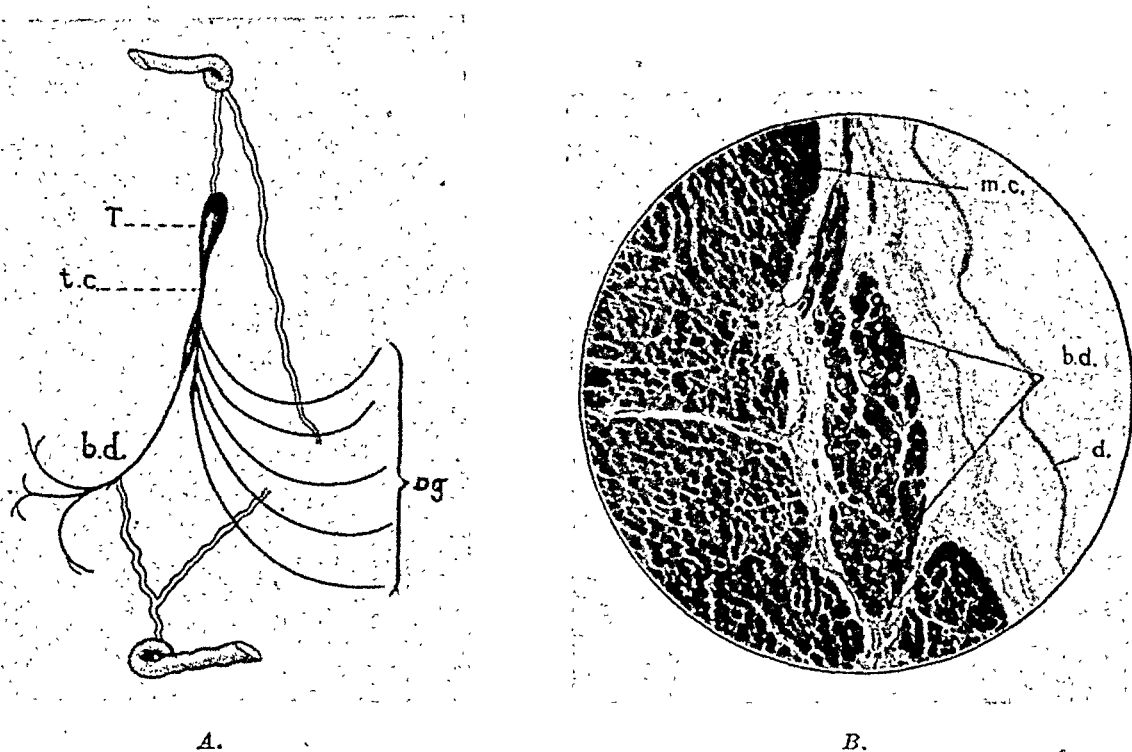

Fig. 7.—The His-Tawara system. (Mahaim.) A, Schematic drawing. B, Microscopic structure—right branch.

In the particular muscle fasciculi which have been thought to be the branches of the His bundle are to be found the blocking lesions which are assumed to be the direct cause of the bundle branch block complexes. We, therefore, logically pass to a review of the studies of the histopathology of the branches of the His bundle.

In order to avoid confusion, the discussion will be limited to the histologic observations in the *common* form of bundle branch block. Those in the case of the less common form are similar. It should be noted that the observations listed have been obtained from a study of serial sections, and that the individual worker who obtained the information stressed the fact that the studies had been done with unusual care. The relation of the blocking lesions which were found in cases of the common form of bundle branch block to the complexes traced by the living heart has been epitomized in Table I. It is clear that, in approximately one-fourth of the cases, no blocking lesions were found,

that in a little more than one-third of the cases the blocking lesions were found on the left side, and that in the remainder they were on the right side.

TABLE I

HISTOLOGIC OBSERVATIONS IN THE COMMON TYPE OF BUNDLE BRANCH BLOCK

AUTHORS	NUMBER OF CASES	RIGHT SIDE OF SEPTUM	LEFT SIDE OF SEPTUM
Eppinger and Stoerck	2	Blocking Lesions	None
Cohn and Lewis	4	No Blocking Lesion	No Blocking Lesion
Oppenheimer and Pardee	1	None	Blocking Lesion
Oppenheimer and Oppenheimer	3	None	Blocking Lesion
Oppenheimer and Oppenheimer	1	Slight Fibrosis	Blocking Lesion
Taussig	1	Blocking Lesion	None
Mahaim	7	Blocking Lesions	Fibrosis
Yater	3	Fibrosis	Blocking Lesions
Yater	1	No Blocking Lesion	No Blocking Lesion
Summation	23	10 Blocking Lesions 5 No Blocking Lesion	8 Blocking Lesions 5 No Blocking Lesion

CONCLUSIONS

From the reviewed observations the following conclusions appear justifiable:

1. The common type of bundle branch block complex represents left ventricular lag; the less common type represents lag of the right ventricle. The many attempts which have been made to group the complexes into logical classes are of scant practical value in the diagnosis and prognosis of cardiac disease.

2. The evidence presented to prove the existence of a special conducting system is irrelevant and immaterial.

3. The microscopic areas of fibrosis which have been found in the upper part of the interventricular septum in cases of bundle branch block bear no causal relation to the grossly abnormal ventricular deflections that have a prolonged QRS interval because:

   a. Such lesions are absent in a considerable number of cases of bundle branch block.

   b. When small fibrous lesions are found in either right or left bundle branch block, they occur with about equal frequency on both sides of the septum.

4. It is, therefore, apparent that further search should be made for the cause of the grossly abnormal complexes which are now thought to indicate bundle branch block.

"NACHHINKEN"

In their earliest experiment on bundle branch block, Eppinger and Rothberger observed that, while the wide diphasic ventricular complexes were being traced, the injured ventricle was dilated and "limped after"

the contralateral ventricle. This "nachhinken" has been noted by practically all experimental observers of bundle branch block. More recently, such delayed activation of the ventricle has been demonstrated by Wilson, Macleod, and Barker,[33] Wolferth and Margolies,[31] and Braun-Menéndez and Solari[32] in cases of human bundle branch block. It is, therefore, apparent that the so-called bundle branch block complexes may be the electrocardiographic manifestation of a "failing" right or left ventricle; if so, any factor or factors which can produce this unilateral lag may be responsible for bundle branch complexes.

Many excellent studies of human bundle branch block have been reported: Carter,[15] Oppenheimer and Rothschild,[14] Willius,[58] Herrick and Smith,[59] and Hill.[60] There is striking uniformity in the clinical observations made by these investigators. It is apparent that human bundle branch block complexes are traced by sick hearts. (The bundle branch block complexes with a short P–R interval are not included in this discussion because the nature of these is different from that of the others.) The factors which have crippled the hearts in cases of bundle branch block are identical with those which lead to cardiac failure, with or without these abnormal electrocardiograms. Thus, when bundle branch block complexes are obtained in the young, they are found in connection with congenital defects, hyperthyroidism, or infections of the heart; after the age of 40 years, they are associated, as a rule, with hypertension, coronary atherosclerosis, or a combination of these conditions. Therefore, it occurred to us that the same factors might bring about bundle branch block complexes whenever they produce failure in one ventricle while the other is relatively normal. Out of these considerations grew the following working hypothesis:

Bundle branch block complexes are caused by:

a. abnormal unilateral strain.
b. unilateral ventricular coronary insufficiency.
c. a combination of (a) and (b).

In our next communication we shall present the evidence that we have obtained pertinent to this hypothesis.

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STUDIES ON UNIPOLAR LEADS

IV. The Effects of Digitalis

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INTRODUCTION

FOR the past three years we have been conducting studies on the use and application of unipolar leads, particularly augmented, unipolar, extremity leads (aV- leads). In several previous publications, the principles and patterns of these leads have been described,[1,2] as well as characteristic patterns with myocardial infarction when standard leads are normal.[2,3]

We felt that this advantage of aV- leads in detecting minimal electrocardiographic changes might be put to further use in the study of other factors affecting the electrocardiogram.

In this paper, our observations on the effects of digitalis on augmented unipolar extremity leads and on unipolar precordial leads are described.

MATERIAL AND METHOD

Although we have on file unipolar records of over 3,000 patients, of whom 500 had been digitalized, for this study we selected and observed 21 cases, both before and after digitalization. Of this group, five had normal hearts, four had rheumatic heart disease, six had hypertensive cardiovascular disease, three had abnormal electrocardiographic patterns without a history of heart disease (cases of severe secondary anemia due to duodenal ulceration), and three were convalescing from recent attacks of myocardial infarction. The acute attack in each of these cases had occurred approximately five weeks previously. None of these patients had ever received digitalis.

Routine digitalization was produced with tablets of powdered *Digitalis purpurea* in the following way: 6 grains were given every eight hours for three doses, then 3 grains a day for four days.

Electrocardiograms were taken a few hours before digitalization and five days later. In all these cases there was a previous electrocardiogram taken before the start of the experiments. Comparison of this with the control electrocardiogram showed, in all cases, no change.

Seven leads were taken. First, the three standard leads. Then, using the author's indifferent electrode of zero potential,[1] aV- leads[1] and a unipolar precordial lead, V_4, with the electrode at the fifth intercostal space in the midclavicular line, were taken.[1,4] All records were taken with the patients recumbent.

In this study we were not interested in the effects of minimal doses of digitalis on the electrocardiogram.

A. Unipolar Extremity Leads:

1. *P Wave and P-R Interval.*—No characteristic changes in the size and shape of the P wave were noted. The P-R interval was, for the most part, not affected by the amount of digitalis used. Occasionally a lengthening of the P-R interval was noted.

2. *QRS Interval.*—No change in the duration of the QRS interval was noted.

3. *Amplitude of the QRS Complex.*—There was no constant pattern of change in the amplitude of the QRS complex; in one lead the amplitude might be larger, and, in another, smaller than before digitalis administration. However, since the amplitude of QRS in unipolar extremity leads varies directly with the electrical axis of the body,[2] we thought it might be interesting to ascertain whether there was any shift of the electrical axis. We therefore calculated the changes in the electrical axis of the heart directly from the aV- leads.[5]

In this series of cases, the average change in angle α was +5°. In five of our records, no appreciable change was noted. In one case, there was a change of –5°. Changes as high as +15° C. were observed in four records.

4. *The Q-T Interval.*—In ascertaining the effect of digitalis on the Q-T interval, recourse was made to the formula of Fredericia,[6] namely, Q-T = 8.22 $\sqrt[3]{\text{R-R}}$,* in which the Q-T interval is described as a function of the ventricular rate.

The Q-T values were calculated as follows: First, the theoretical value was calculated by Fredericia's formula. This was compared to the actual value, read directly from the electrocardiogram. The relation of the actual to the theoretical Q-T value was then expressed as a percentage. This procedure was carried out with the records taken both before and after digitalization. This permits comparison of the two percentages. In Table I, these values are given for the cases illustrated.

Without exception, the Q-T interval was shortened, proportionately, more than could be expected from any change in ventricular rate. In fact, since slowing of the rate was the usual occurrence, lengthening of the Q-T interval would have been expected from the formula.

5. *The RS-T Segment and the T Wave.*—After the administration of digitalis, the RS-T segment and the T wave of the aV- leads always tend to deviate in the direction opposite to that which T originally had, irrespective of the characteristics of the electrocardiogram. Generally, this is also in the direction opposite to that of the main ventricular complex.

The following is a description of these changes in more detail in a typical case (Fig. 1): If T is originally (+), the RS-T segment, begin-

*The Q-T and R-R intervals are expressed in terms of hundredths of a second. Thus, 0.36 second is expressed 36.

CASE NUMBER		ACTUAL Q-T INTERVAL (SEC.)	VENTRICULAR RATE	R-R INTERVAL (SEC.)	PERCENTAGE OF FORMULA $Q\text{-}T = 8.22\sqrt[3]{R\text{-}R}$ (%)
700	before	.32	88	.64	97.3
	after	.28	75	.80	79.1
741	before	.38	68	.88	107.2
	after	.36	60	.88	94.7
702	before	.42	55	1.04	108.6
	after	.36	59	1.01	94.1
706	before	.36	60	1.00	109.1
	after	.32	60	1.00	96.7
721	before	.42	75	.80	119.0
	after	.32	75	.80	90.3
740	before	.36	60	1.00	94.6
	after	.34	65	.92	75.3
749	before	.36	75	.80	101.1
	after	.34	78	.76	97.7

*For details see text.

ning slightly below the isoelectric line, slants obliquely in a (−) direction and fuses with T, which has completely changed its own direction and is now also (−). There is then an abrupt rise to the isoelectric line. If T is (−), the reverse conditions hold.

These changes may or may not be apparent in all three aV- leads. Furthermore, the RS-T slope is often not so oblique, and may have a gentle curve downward (Fig. 4, aVf lead), or a gentle upcurve (Fig. 7, aVf lead). When minimal changes are present, the only evidence may be a decrease in the amplitude of T. This occurs irrespective of whether T had originally been (÷) or (−) (Fig. 5, aVf Lead; Fig. 2, aVl lead).

As was just mentioned, these changes were found in the electrocardiograms of both normal and abnormal hearts, except that, in our three cases of recent myocardial infarction, the changes were minimal and consisted for the most part of slight diminution of the T wave. In one case there was a reversal of T.

When the changes in the aV- leads are compared with those in the standard leads, the results are very interesting.

In Case 702 (Fig. 3), the standard leads showed a diminution of the T wave, whereas the aV- leads not only showed this, but, in the aVl lead, there was complete reversal of the direction of T, which became (÷) after being deeply (−).

In Case 706 (Fig. 4), again, there was only a slight decrease in the amplitude of T in Leads I and II, whereas, in the aVf lead, T became (−) instead of (÷).

In Case 740 (Fig. 6), the patterns of left ventricular preponderance showed but little evidence of any digitalis effect, whereas, in the aVf lead, T changed from (÷) to (−).
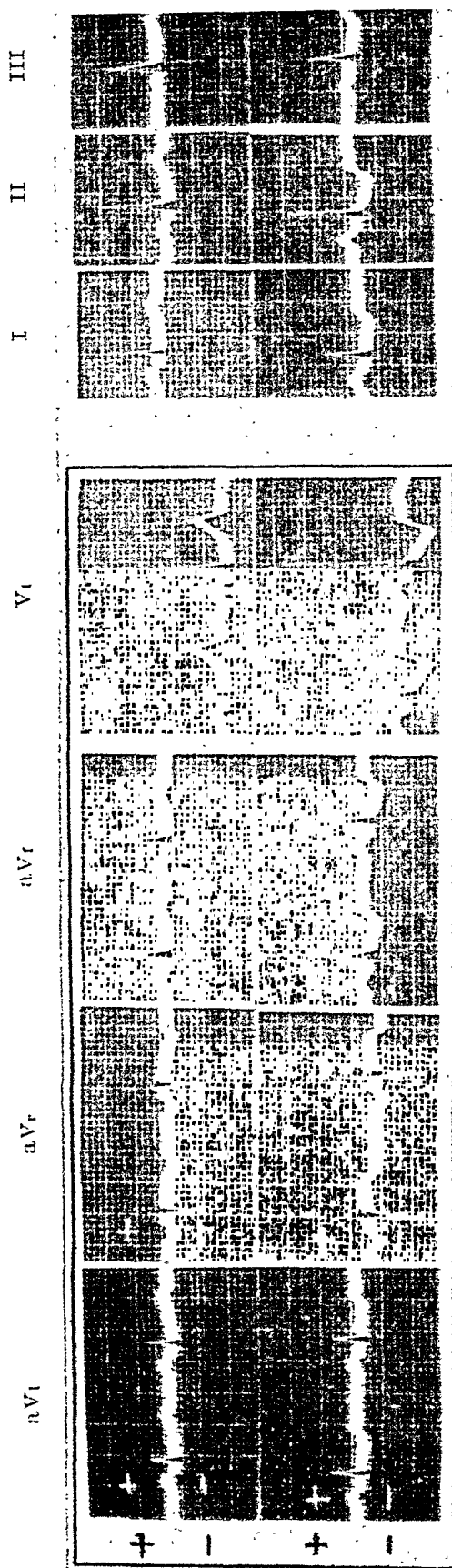
Fig. 1.—Case 700, male, 31 years of age, normal.

Figs. 1 to 7

The effects of digitalis on augmented unipolar extremity leads (aV- leads*) and unipolar precordial leads.
Upper row—before digitalization.
Lower row—after digitalization.

*In all illustrations in this article the aVl lead records potentials from the left arm, the aVr lead records potentials from the right arm, and the aVf lead records potentials from the left leg.
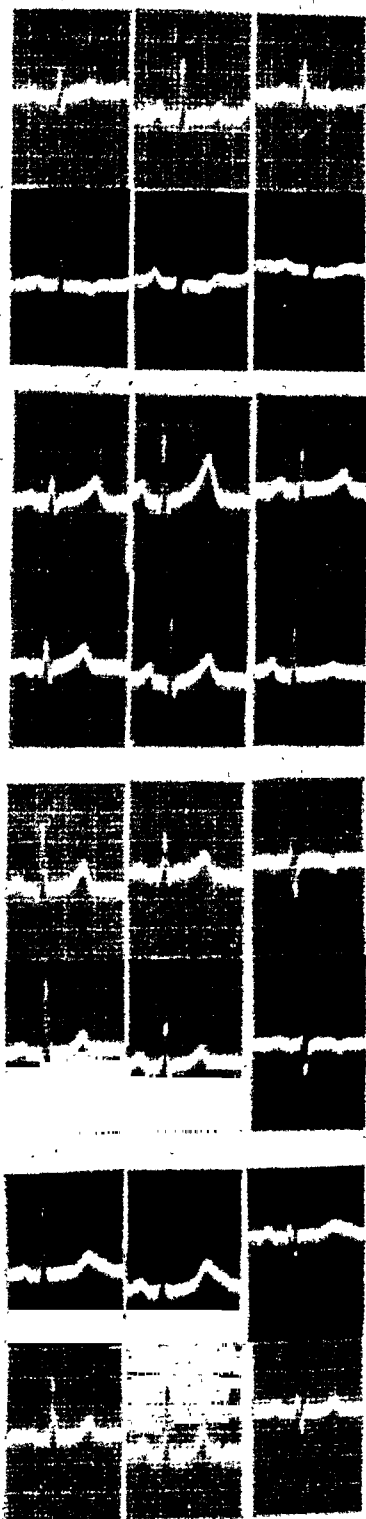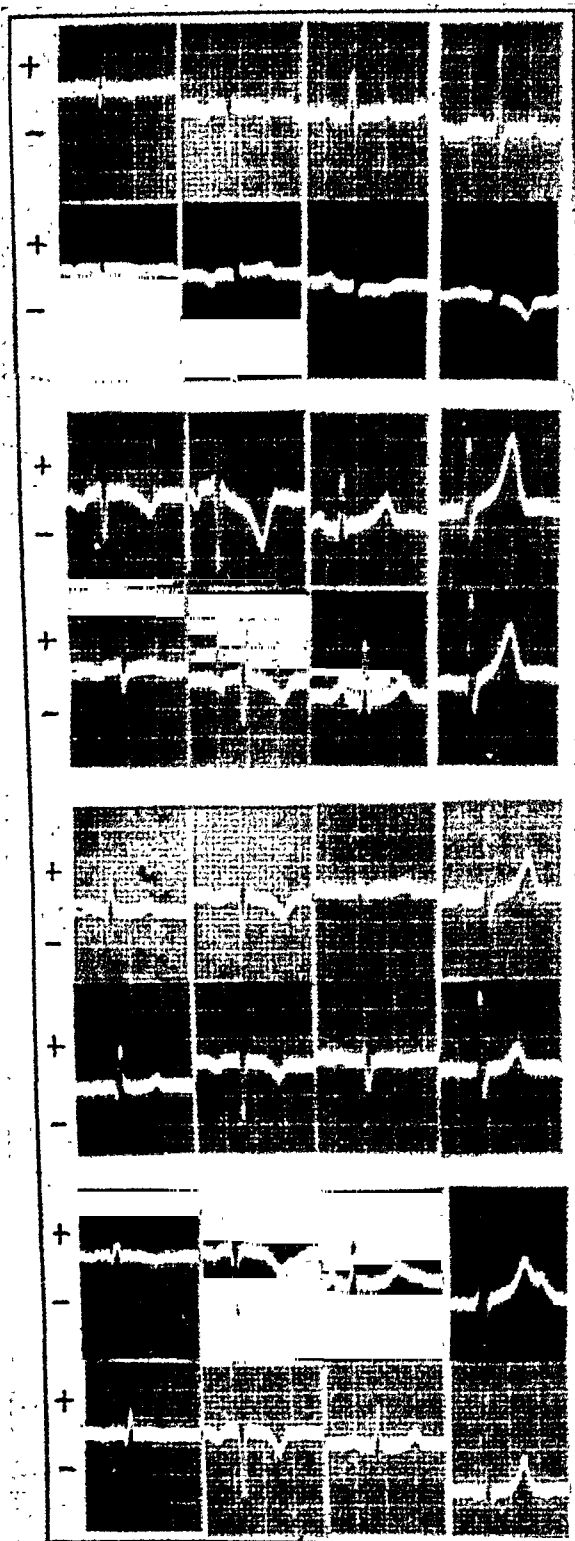
Fig. 2.—Case 748, female, 43 years of age, rheumatic heart disease, mitral insufficiency and stenosis.

Fig. 3.—Case 702, male, 32 years of age, bleeding duodenal ulcer, secondary anemia.

Fig. 4.—Case 706, male, 51 years of age, normal.

Fig. 5.—Case 721, male, 50 years of age, bleeding duodenal ulcer, secondary anemia.

Also, in Case 749 (Fig. 7), another example of left ventricular preponderance, the T of the aVf lead showed a very definite change from (−) to (+) polarity, although the standard leads before and after digitalization were quite similar.

B. Unipolar Precordial Leads: The P wave, P-R interval, QRS interval, and Q-T interval were the same as in aV- leads.
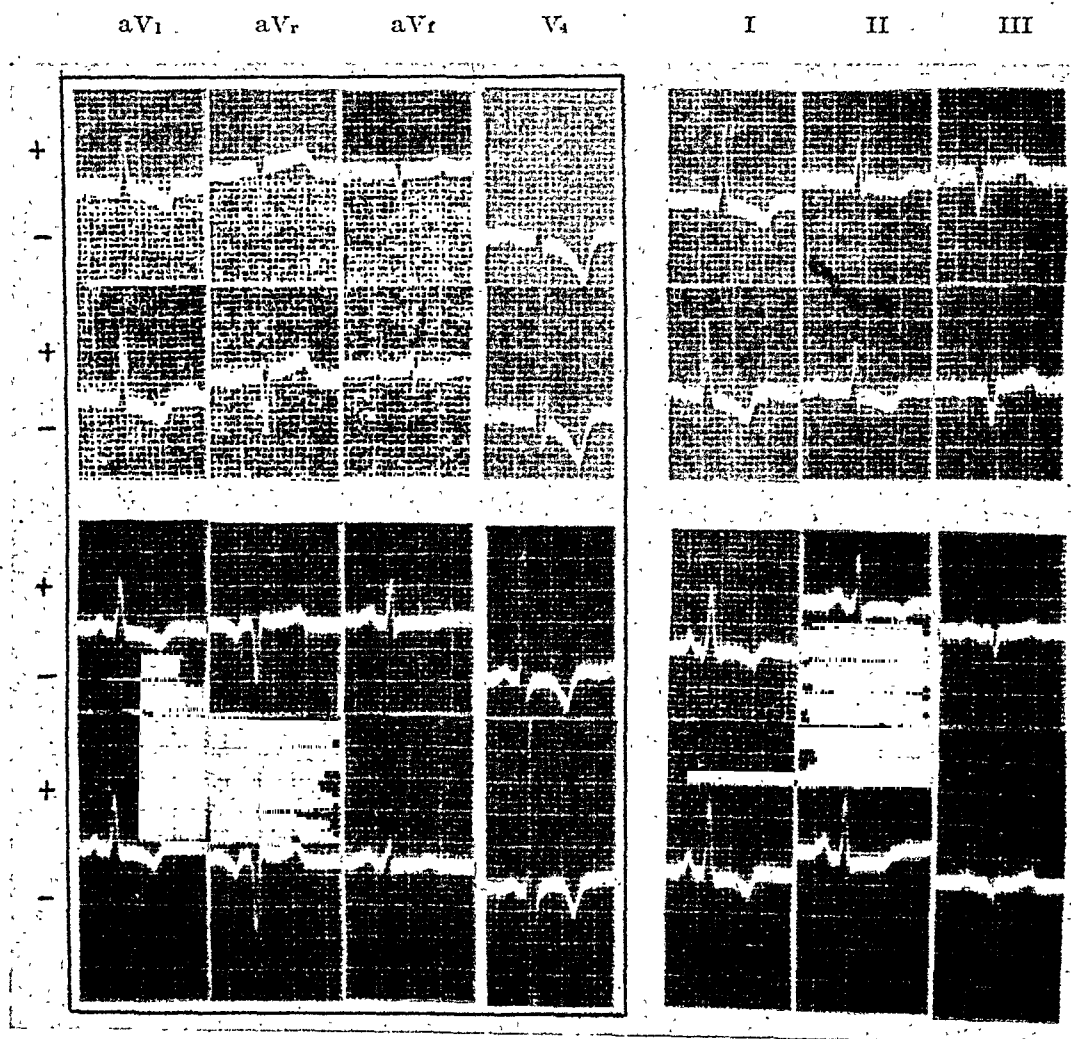
Fig. 6.—Case 740, female, 47 years of age, hypertension.
Fig. 7.—Case 749, female, 63 years of age, hypertension.

1. *Amplitude of the QRS Complex.*—No characteristic change in the amplitude of QRS in the precordial leads was noted. In many of the records there was a slight decrease.

2. *The RS-T Segment and T Wave.*—In precordial leads, digitalis always causes the RS-T segment and T wave to move in a downward (negative) direction. If the RS-T and T are originally directed downward, as in cases of ventricular preponderance, the only effect is that the angle at which the RS-T segment becomes (−) is made more acute (Figs. 6 and 7). When T is upright, the changes are very similar to those in the aV- leads with an upright T. A slight effect consists merely in a decrease of the amplitude of T (Fig. 3), whereas, with maximal

effect, the RS-T segment, beginning below the isoelectric line, runs obliquely downward, fuses with the (−) T, and sharply rises to the isoelectric line (Fig. 1). The slope of the RS-T may be straight (Fig. 1), or may have a gentle downward curve (Fig. 2).

3. *The U Wave.*—The U wave, usually not conspicuous, was present in the precordial leads in seven of our cases. The effect of digitalis on the U wave was as follows: in three there was no change, in two, there was a slight diminution in the amplitude of U, and, in two cases, U became (−) instead of (+) (Fig. 5):

DISCUSSION

Our results compare favorably, in so far as they can be compared, with those reported in the literature for the standard and ordinary precordial leads. There have been conflicting reports concerning the effect of digitalis on the amplitude of the QRS in standard leads.[7, 8] Our data, showing that there is a change in the electrical axis, probably explain this.

The decrease in the Q-T interval is generally regarded as a manifestation of digitalization,[8] although this, too, has been questioned,[9] and inversion of T and the depression of the RS-T segment were described many years ago.[10, 11]

With respect to the effects of digitalis on precordial leads, although varied changes have been described, such as raising or lowering of the RS-T segment and increased or decreased T waves,[12] our results are similar to those currently accepted.[13]

CONCLUSIONS

We find that the effects of digitalis on the unipolar leads of the electrocardiogram are quite constant, and occur irrespective of the nature of the cardiac condition or of the previous electrocardiographic pattern.

In augmented unipolar extremity leads (aV- leads), both the RS-T segment and the T wave tend to deviate in a direction opposite to that in which T was previously directed. Thus, if T had been (+), the direction of deviation is (−), and vice versa. When this is marked, RS-T moves obliquely downward or upward, as the case may be, fuses with T, and then abruptly runs to the isoelectric line. Along with these changes, there may be an increase in the P-R interval, a decreased Q-T interval, and a slight shift in the electrical axis of the heart, usually in a clockwise direction. Minimal T changes consist in merely a decrease in amplitude.

It was also observed that, in cases in which the standard leads showed only inconstant or no changes, in one or more of the aV- leads a characteristic and definite reversal of direction of T was observed.

In unipolar precordial leads the changes were similar, but the direction of deviation was always in a (−) downward direction. A decrease in the amplitude of U may also be observed, and also a reversal of its polarity.

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THE EFFECT OF CHRONIC CORONARY SINUS OCCLUSION ON THE VASCULARITY OF THE DOG'S MYOCARDIUM

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IN THE search for effective therapeutic measures against coronary disease, attention has turned in recent years to surgical procedures aimed at providing the heart with an additional blood supply from extracardiac sources.

In 1935, Gross and Blum[1] demonstrated by an injection and roentgenographic technique that occlusion of the coronary sinus produced an augmentation of the intrinsic arterial vascular bed. In dogs with previous coronary sinus occlusion, the incidence of infarction after ligation of the left anterior descending coronary artery was reduced.

Gross, Blum, and Silverman,[2] in subsequent experiments, found that the mortality after ligation of the left anterior descending coronary artery was reduced by previous partial coronary sinus occlusion, but not by total sinus occlusion. The size and frequency of infarction was reported to be diminished, and the arterial vascular bed enlarged, in hearts with partial sinus occlusion.

Electrocardiographic observations made after sinus occlusion yielded transient abnormalities which were ascribed by Gross and his co-workers[3] to myocardial ischemia due to venous congestion. The dilatation and cyanotic appearance of the left ventricle after obturation of the coronary sinus is in consonance with this view.

The experiments to be described were undertaken in order to ascertain whether or not the augmentation in the coronary arterial bed which has been noted within a period of several weeks after coronary sinus occlusion persists over a period of years.

METHODS

Adult mongrel dogs were anesthetized by giving nembutal intraperitoneally (25 mg. per kilogram). The surgical approach to the sinus was essentially that employed by Gross and his co-workers.[2, 4] Procaine solution, applied to the surface of the heart as described by Mautz,[5] eliminated cardiac irregularities produced by manipulation. A method of sinus closure was used which, it was hoped, would be gradual and progressive, and circumvent the effects of complete and sudden ligation. Although it was subsequently shown by Beck[6] that the high mortality after complete coronary sinus ligation in normal dogs observed by Gross[2] need not occur, this gives no assurance that a heart already impaired by coronary disease could survive the immediate deleterious effects of acute venous stasis.

Accordingly, the coronary sinus was picked up gently in an Allis forceps at a point about 1 cm. from its entrance into the right atrium. A second Allis was then placed as completely around the sinus as possible. A small, c-shaped, metal clip, about ⅛ inch in width, and large enough in circumference to fit around the sinus and perisinus fat, was grasped in a Kocher's forceps and slipped around the vessel just at the side of the Allis forceps near the entrance of the sinus into the right atrium. The ends of the clip were serrated to prevent slipping. After being placed around the coronary sinus, the clip was compressed until the sinus beyond the clip just began to bulge. The pericardium and chest were then closed.

Ringer's mixture

Syringe

Mercury manometer

Heart

Injection mass   Water bath
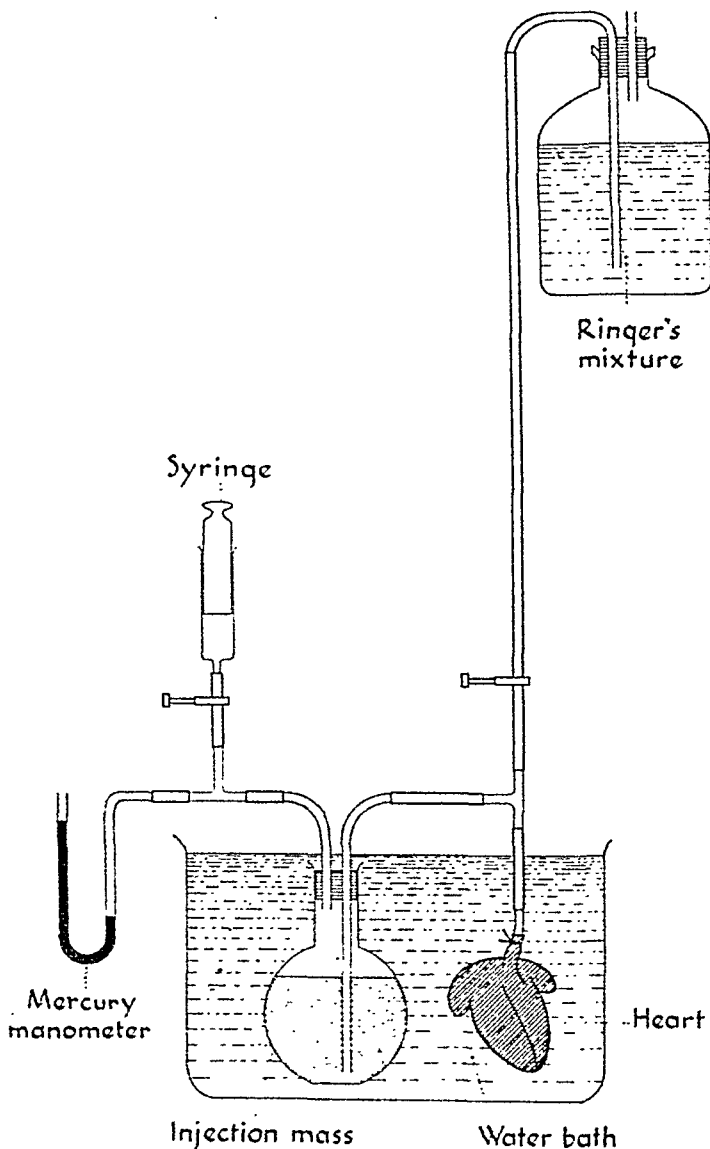
Fig. 1.

Six animals were prepared in this fashion. One died of a wound infection on the seventh postoperative day, and one of distemper on the twelfth day after operation. The other four survived, and were in good health when sacrificed three years later. The simplicity of the procedure is indicated by the absence of mortality due to the operation itself in the first six animals so treated.

After a period of three years, the animals were anesthetized with ether, and the hearts were excised widely in order to leave the atria in-

tact, and then injected, dissected, and roentgenographed in a manner essentially similar to that described by Schlesinger,[7] except for the injection. In the method used, the injection mass was introduced via the aorta, rather than the coronary arteries, for this was found to be simpler and more dependable; the right coronary artery frequently arises by multiple ostia, and is difficult to cannulate in the dog.

The aorta was cannulated under saline, care being taken to prevent the entrance of air into the system. The coronary arteries were then flushed with warm Ringer's fluid to remove the blood. After this, the heart was suspended in a saline bath at 45° C., the tube from the Ringer's fluid reservoir was clamped, and a side arm leading to the flask containing the injection mass was opened. The injection mass was then introduced as indicated in Fig. 1, in which a diagram of the method of injection is presented. A pressure of 150 mm. Hg was maintained during the injection and for a period of several minutes after the mass had ceased to move forward. Then the short segment of rubber tubing just above the aortic cannula was clamped and disconnected from the system, and, while pressure was still being maintained in the aorta, the heart was placed in the icebox until the injection mass had set. The procedure from this point forward was carried out as indicated.[7]

Nine control hearts were prepared in addition to the four experimentals.

Besides the roentgenograms, microscopic sections were made from the left ventricles of the control and experimental hearts, and the coronary sinuses in the experimental hearts were carefully dissected.

<center>RESULTS</center>

Of the four experimental hearts, only one showed a completely occluded sinus. The degree of closure was estimated at 30, 50, and 90 per cent in the other three hearts. In those with 30 and 50 per cent occlusion, the clips had not bent symmetrically on compression, and therefore did not completely surround the sinus. Although they occupied approximately the same position with relation to the vessel, there was an obvious difference in the degree of occlusion; this was probably accounted for by the difference in the material from which the clips were made. That on the more patent sinus had been made of silver, whereas all the others had been fashioned by cutting stainless skin clips down to size and bending them appropriately. This latter material apparently called forth a more marked connective tissue reaction than did the silver.

Thus, fortuitously, a series ranging from slight to complete closure of the coronary sinus was obtained. Examination of the roentgenograms of the injected specimens in no case showed augmentation of the arterial bed when compared with the controls. (In making the comparison, the number of small vessels visualized served as the criterion.) Indeed, the experimental specimens, as a group, appeared definitely less vascular than the controls, as a group, although there were less vascular hearts in the control group with which those which showed only partial

sinus occlusion compared favorably. This was not true, however, of the specimen with complete sinus occlusion, in which the least vascularity was demonstrated.
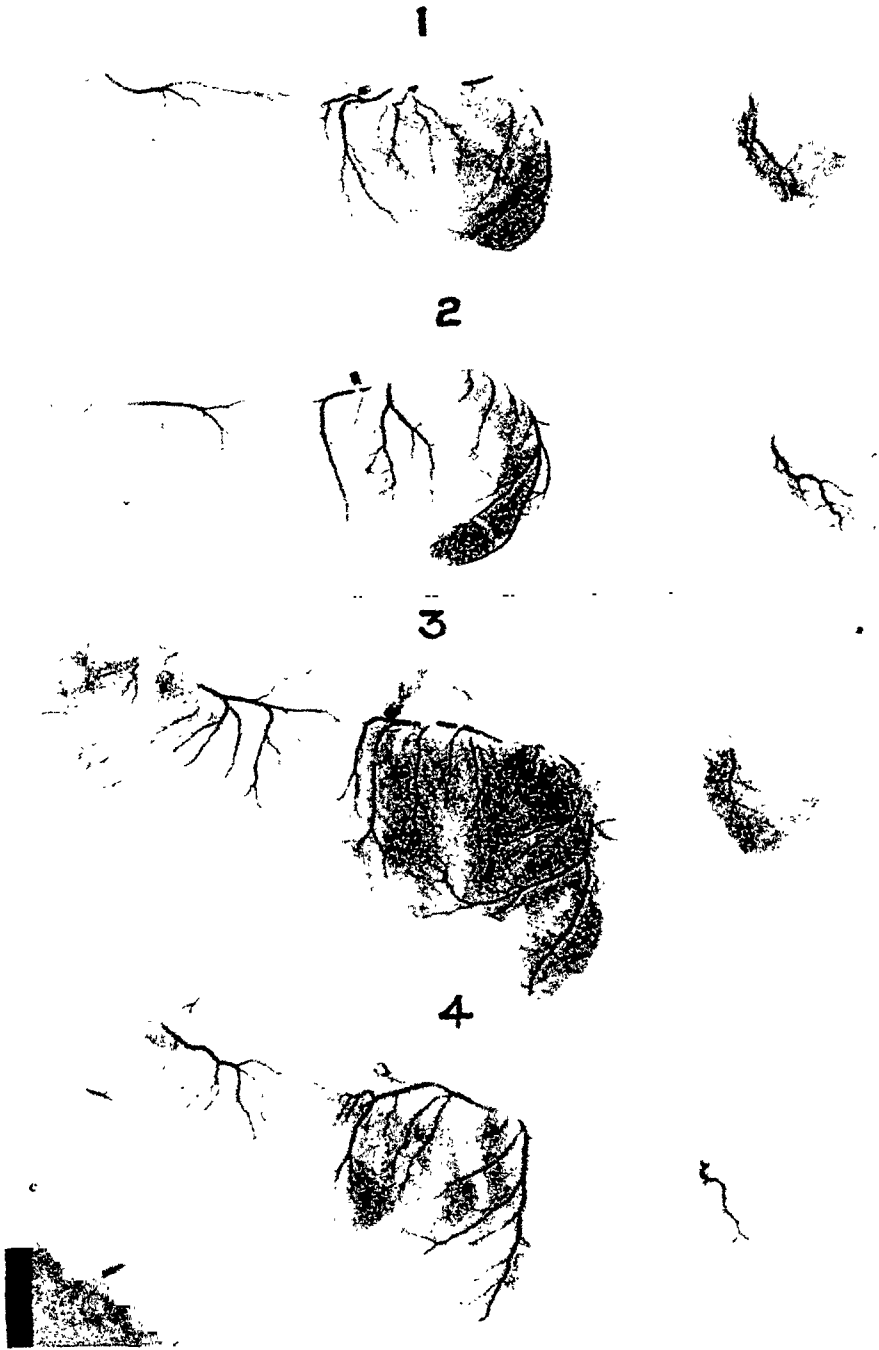

Fig. 2.

Within the experimental series itself, the vascularity appeared to vary inversely with the degree of obturation of the coronary sinus. Although the method, as a quantitative measure of the coronary bed, leaves much to be desired, and although it cannot be said with certainty that the differences here noted are not due to some unrecognized systematic discrepancy, there can be no doubt that so considerable an augmentation of the coronary arterial bed as that demonstrated by Gross,

et al.,[1,2] after recent coronary sinus occlusion could not have been missed by this procedure, and certainly did not exist in these specimens.

Reproductions of the roentgenograms of the four experimental hearts and three of the controls are presented in Figs. 2 and 3. Observations on the experimental hearts are summarized in Table I.

TABLE I

HEART NUMBER	DEGREE OF SINUS OCCLUSION (%)	ROENTGENOGRAPHIC APPEARANCE OF VASCULAR BED	RELATIVE DENSITY OF THE VASCULAR BED*
1	50	Comparable to less vascular control hearts	+++
2	90	Comparable to less vascular control hearts	++
3	30	Comparable to moderately vascular control hearts	++++
4	100	Not as vascular as the least vascular control heart	+

*As compared to the other experimental hearts.
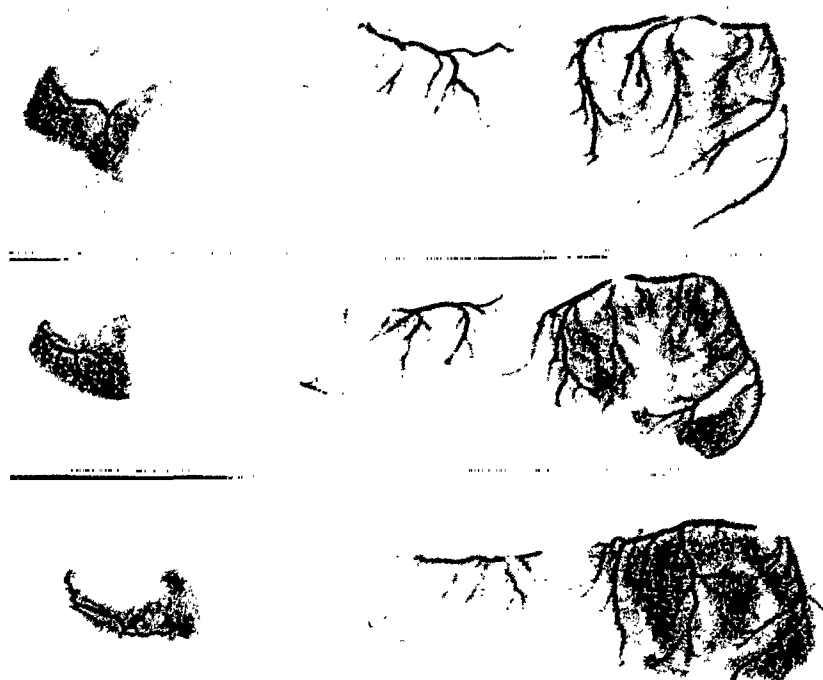
Fig. 3.

It may be observed that all the hearts shown in the figures (and this is true of all the specimens studied) are of the type with a predominant left coronary artery, previously described by Schlesinger[4] as typical in the dog.

Finally, it should be stated that careful study of the microscopic sections made from the control and experimental hearts showed no demonstrable differences.

DISCUSSION

Reports made available since the present study was undertaken lend some support to the observations just described. Gregg and his co-workers[9, 10, 11] have shown that the backflow from a ligated coronary artery peripheral to the point of ligation is considerably above the normal if the coronary sinus is ligated simultaneously. However, retrograde flow is only slightly increased if coronary sinus ligation is carried out thirty days prior to arterial occlusion. Sinus occlusion, however, was found to influence favorably the mortality from arterial occlusion.

Beck[6] also found a definite decrease in the mortality rate after coronary artery occlusion if the coronary sinus is also ligated. He reported, however, that the beneficial effect of venous ligation is least when vein and artery are closed at the same operation, that it is greatest when carried out six weeks prior to ligation of the artery, and decreases again when a longer interval (four months) elapses between the two procedures. Beck, unlike Gross, et al.,[1, 2] always found infarcts after arterial occlusion, but judged them to be smaller in size when sinus ligation had been done previously.

Obviously, before coronary sinus closure can be finally evaluated as a protective measure against arterial occlusion, the mortality, induced by the latter procedure when it is carried out one or more years after the former, must be ascertained.

The observations recorded to date lend slight support to the suggestion that coronary sinus occlusion might be of value as a therapeutic procedure in coronary disease by permanently increasing the basic vascular bed.

SUMMARY

Dog hearts, after three years of graded coronary sinus occlusion, varying from slight to complete closure, did not exhibit the augmentation of the coronary arterial bed which has been demonstrated by others within a period of days to weeks after obturation of this vessel. On the contrary, myocardial vascularity appeared reduced, if anything, as a result of this procedure.

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PERICARDITIS ASSOCIATED WITH PRIMARY ATYPICAL PNEUMONIA

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A SURVEY of the admissions to the cardiovascular section of the Schick General Hospital has revealed a small group of cases of pericarditis which did not conform with any accepted etiologic classification. Upon reviewing these cases, it was found that all the patients had a concomitant or antecedent primary atypical pneumonia. A survey of the available literature revealed reports of isolated cases of pericarditis after upper respiratory infections,[1-3] but failed to disclose any report of pericarditis associated with primary atypical pneumonia. It was thought, therefore, that it would be of interest to report three such cases which have been under our observation.

CLINICAL COURSE

These three patients were men, and ranged in age from 19 to 27 years. Each illness began with an upper respiratory infection, characterized essentially by fever, sore throat, cough, and a variable degree of expectoration. Within a few days, when these patients appeared to have fully recovered, they suddenly developed an exacerbation of their symptoms, associated with pain in the anterior part of the chest which was aggravated by deep inspiration. In two of the cases, teleoroentgenograms taken at this time showed areas of pneumonitis interpreted as primary atypical pneumonia. The clinical course of the third patient was similar, but definite roentgenologic evidence of pneumonitis did not appear until six weeks later, although prominent hilar shadows and increased bronchovascular markings were present throughout this period. Roentgenologic evidence of pneumonitis persisted from twenty-seven to ninety-eight days. In all the cases, at some time during the course of the pneumonia, clinical signs of pulmonary disease, consisting primarily of moist râles over the involved areas, were detectable. As has been noted previously in primary atypical pneumonia,[4] the roentgenologic evidence of pneumonitis was more extensive than was suspected from clinical examination. At the onset of the pneumonitis a leucocytosis ranging from 15,000 to 18,000 was present in all three cases. The differential count was not remarkable. Blood cultures and typing of the sputum for pneumococci were negative in all the cases. Throat cultures failed to reveal any specific bacterial organisms. Urinalyses and Kahn tests were consistently negative. Sedimentation rates were not ascertained at this time.

The interval between the onset of the upper respiratory infection and appearance of the pericarditis ranged from seven to forty-one days. The pericarditis was ushered in by an increase in the pulse rate in all cases from a previous level of 75 to 90 per minute to a range of 100 to 130 per minute, accompanied by a rise in temperature of 1.5° to 2° F. The respirations showed little change. In two cases a pericardial friction rub was audible at the onset; in one case the friction rub was audible for two days, and in the second case it was present for seven days. Typical electrocardiographic changes of acute pericarditis appeared simultaneously. In the other case no pericardial rub was detected and the diagnosis was made only by serial electrocardiograms. In the two cases in which a friction rub was audible, pain was present in the left anterior part of the chest, and, in one, this was associated with pain in the left shoulder. There was no significant alteration in the blood pressure during the course of the pericarditis. The clinical appearance of the patients during the period of pericarditis was variable. Two patients became apprehensive as the result of consciousness of a rapid heart rate. The remaining patient (J. H. B.) was more acutely ill and toxic. At no time were any of the patients in a critical condition.

The leucocytosis, which was present at the time of the pneumonitis, had begun to subside. With the onset of pericarditis, the leucocyte count increased from an average of 12,000 to 15,500. In two of the three cases, the sedimentation index was increased during the course of the pericarditis. At the onset of the pericarditis, the electrocardiogram in two of the three cases showed R-T elevations in the limb leads and Lead IV F which were consistent with the acute stage. In the third case no tracing was taken during the acute phase. The duration of this period varied from seven to fifteen days. In all three cases, the subacute pattern was present, which was characterized by T-wave inversion in some or all of the standard leads and Lead IV F. This subacute stage lasted from thirty-four to sixty-eight days. In all the cases, with the healing of the pericarditis, the R-T segments became isoelectric and the T waves, upright. Serial roentgenograms of the heart revealed enlargement of the cardiac silhouette in only one case. This amounted to 14 per cent, and it disappeared in twenty-seven days.

CASE REPORTS

CASE 1.—H. A. H. aged 19 years. The family and past history were noncontributory. On February 21, 1943, the patient was hospitalized with a sore throat, headache, cough, and chilliness. On admission his temperature was 102°, his pulse rate was 120, and the respiratory rate was 24. The pharyngeal structures were deeply injected. The remainder of the physical examination was not remarkable. He appeared to improve, but Feb. 27, 1943, he developed fever, pain in the chest, and cough, and roentgenologic studies at this time revealed patchy infiltration in the lower anterior part of the left upper lobe; this was interpreted as primary atypical pneumonia (Fig. 1). The leucocyte count

at this time was 14,000. Within three days the patient improved and became afebrile. On March 1, 1943, the patient again complained of pain in the left anterior part of the chest, and developed a temperature of 102.6° and a pulse rate of 110. A pericardial friction rub was audible at this time and persisted for two days. The temperature became normal in forty-eight hours. The leucocyte count rose to 16,350; the differential count was not remarkable. The electrocardiogram on March 1, 1943, revealed R-T elevation diagnostic of the acute stage of pericarditis (Fig. 2). This persisted until March 16, 1943, when the subacute stage, characterized by T-wave inversion in Leads I and IV F, appeared. The electrocardiogram returned to normal on April 19, 1943, giving a total duration of fifty days of graphic evidence of pericarditis. Roentgenologic evidence of the pneumonitis persisted until June 5, 1943, or a total of ninety-eight days. The sedimentation rate was elevated until May 20, 1943. Sputum examination for pneumococci, throat cultures for specific bacterial organisms, and blood cultures were negative.

A. B. C.
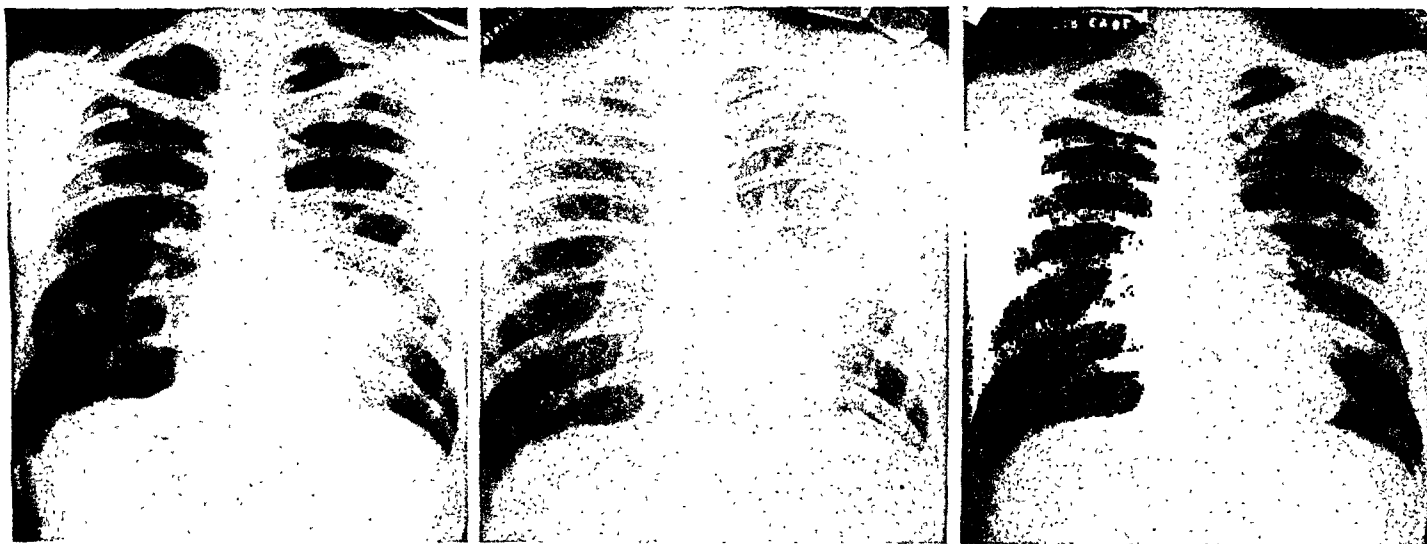
Fig. 1.—Case of H.A.H. A, Roentgenogram taken Feb. 28, 1943, illustrating infiltration of the left hilum and the lower portion of the left upper lobe. B, Roentgenogram taken March 16, 1943, illustrating further spread of the pneumonitis. C, Roentgenogram taken June 5, 1943, illustrating complete resolution of the pneumonic process.

CASE 2.—P. E. J., aged 27 years. The family and past history were noncontributory. On Feb. 10, 1943, this patient developed an upper respiratory infection. His symptoms persisted, and hospitalization was necessary on March 9, 1943. On admission his temperature was 104.2°, his pulse rate, 120, and his respiratory rate, 26. Except for injection of the pharynx, the physical examination was negative. A roentgenogram of the chest revealed patchy areas of pneumonitis in both lower lobes, more marked on the left; this was diagnosed as primary atypical pneumonia (Fig. 3). The leucocyte count was 18,300, with a normal differential. The patient appeared to improve, and, by March 18, 1943, he was afebrile and the leucocyte count had fallen to 11,650. On March 23, 1943, the pulse rate increased from a previous level of 90 to 120. Within twenty-four hours it rose to 140, and there was an associated rise in temperature from 98.6° to 100°. At the same time the patient complained of weakness and palpitation. He remained
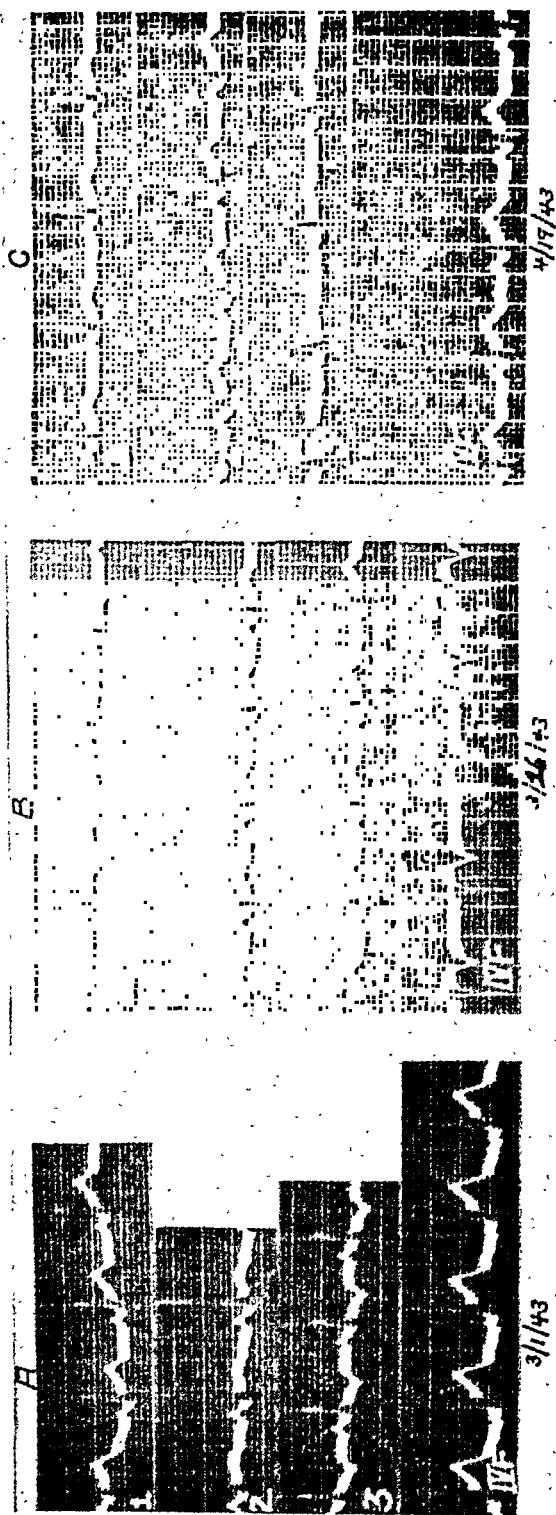
Fig. 2.—Case of H.A.H. A, ECG illustrating the onset of acute pericarditis; R-T elevation in Leads, I, II, and IV F. B, The subacute stage, with T-wave inversion in Leads I and IV F. C, The healed stage, with return of the ECG to normal.

febrile for four days. An electrocardiogram, taken March 30, 1943, showed inversion of the T waves in the standard leads and Lead IV F which was compatible with the diagnosis of pericarditis in the subacute stage (Fig. 4). The leucocyte count during this period rose to 15,650, and the sedimentation index was increased. Electrocardiograms were taken at frequent intervals, and did not become normal until June 7, 1943, making a total of sixty-eight days of electrocardiographic evidence of pericarditis. At no time during the illness was a pericardial friction rub audible. Roentgenologic evidence of pneumonitis persisted for twenty-seven days. Sputum examination for pneumococci, throat cultures for specific bacterial organisms. and blood cultures were negative.
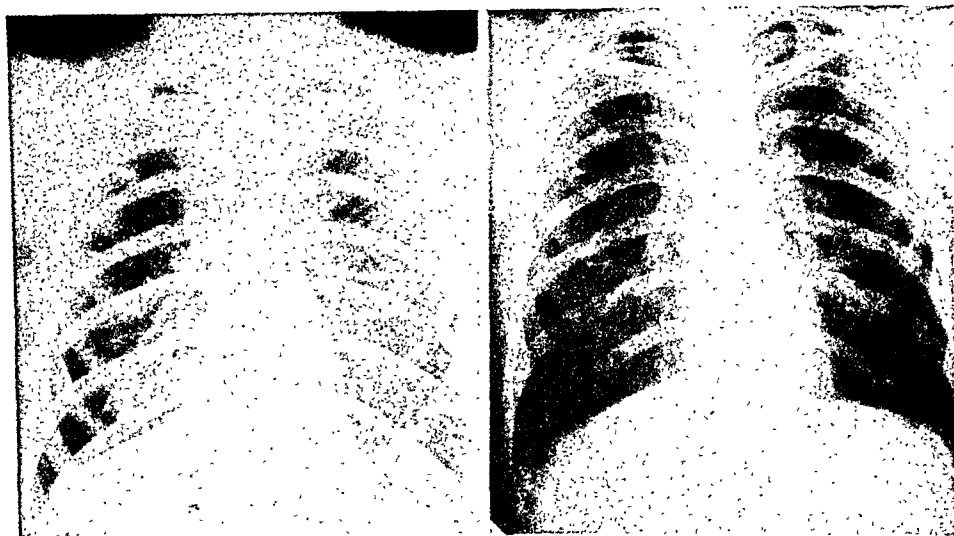
Fig. 3.—Case of P.E.J. A, Roentgenogram taken March 22, 1943, illustrating areas of pneumonitis in both lower lobes, more marked on the left. B, Roentgenogram taken in April, 1943, illustrating complete resolution of the pneumonic process.

CASE 3.—J. H. B., aged 27 years. The family and past history were noncontributory. On April 5, 1943, the patient was hospitalized because of mumps. One week later, while his symptoms and signs were subsiding, he developed cough, with expectoration of mucus, associated with a sharp rise in temperature to 102°. The pulse rate was 100 and the respiratory rate was 22. Physical examination was negative except for an injected pharynx. The leucocyte count at this time was 13,850. On April 19, 1943, he complained of severe substernal pain aggravated by deep inspiration and accompanied by pain in the left shoulder. At this time a pericardial friction rub was audible and persisted for one week. The temperature rose from a previous level of 101° to 103.8°, and the pulse rate increased from 65 to 105. The leucocyte count rose to 16,450, and the sedimentation index was normal. The electrocardiogram on April 20, 1943, revealed R-T elevation in Leads I, II, III, and IV F which was consistent with the acute stage of pericarditis (Fig. 5). A chest roentgenogram did not show any definite evidence of pneumonitis at this time. The electrocardiogram showed abnormalities characteristic of pericarditis until July 6, 1943, making a total duration of seventy-nine days for the period of pericarditis. Frequent roentgenograms of the chest were taken, and, although the hilar markings showed increased prominence, definite pneumonitis was not apparent until June 6, 1943 (Fig. 6). Roentgenologic evidence of pneumonitis persisted until
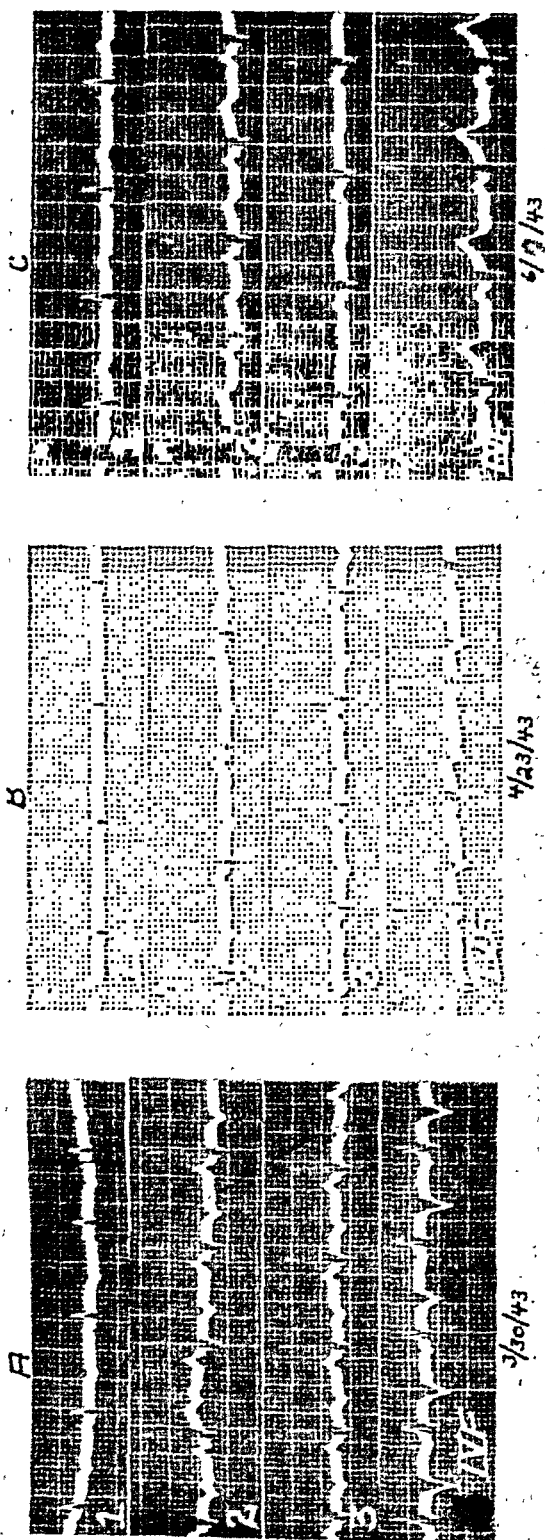
Fig. 4.—Case of P.E.J. A, ECG one week after onset of acute pericarditis, showing T-wave inversion in all leads. B, ECG illustrating healing. The T wave in Lead I has become upright and the T wave in Lead IV F has become diphasic. C, ECG showing the healed stage, with return to normal.
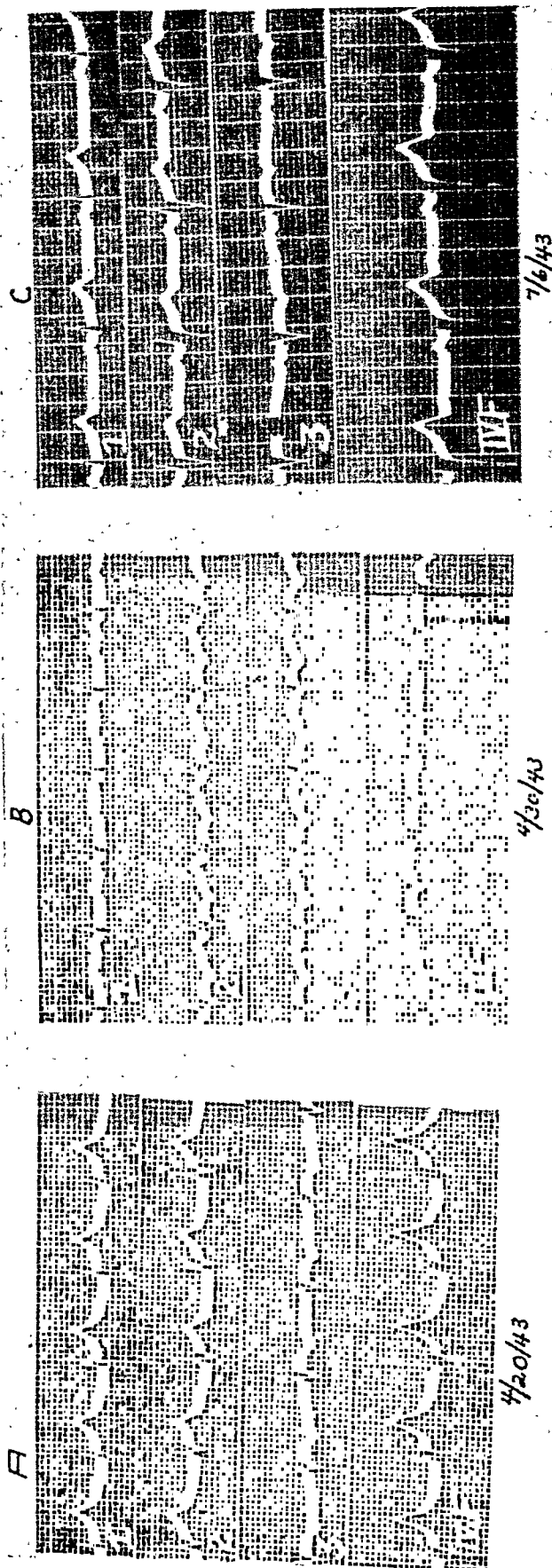
Fig. 5.—Case of J.H.B. *A*, ECG illustrating the onset of acute pericarditis; R-T elevation in all leads. The terminal portion of the T wave in Lead III shows early inversion. There is low voltage in the standard leads. *B*, The subacute stage, with T-wave inversion in Leads II, III, and IV F. *C*, The healed stage, with return of the RS-T segments and T waves to normal.

Aug. 5, 1943, or a total of sixty days. Sputum examinations for pneumococci, throat cultures for specific bacterial organisms, and blood cultures were negative.

A.   B.
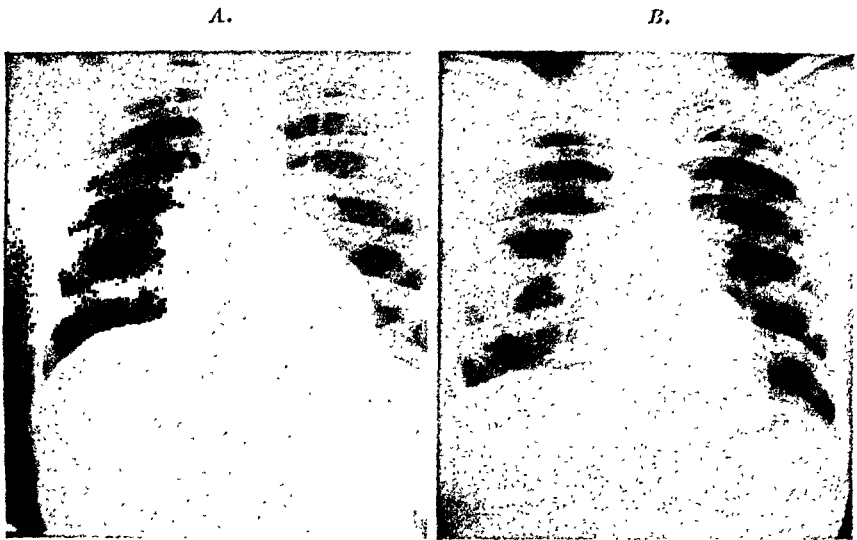
Fig. 6.—Case of J.H.B. *A*, Roentgenogram taken April 20, 1943, illustrating increased bronchovascular markings in the right hilar area. *B*, Roentgenogram taken June 12, 1943, illustrating pneumonitis in the hilar region and the periphery of the right lung.

DISCUSSION

It is thus apparent that pericarditis may occur in association with primary, atypical pneumonia. Clinically these patients present a paucity of symptoms and signs, and the diagnosis depends in large measure on changes in the electrocardiogram. A pericardial friction rub, which is diagnostic, may be present but may not be detected unless the patient is seen and examined at very frequent intervals. It is probable that additional cases would be uncovered if serial electrocardiograms were taken in all cases of primary atypical pneumonia. This condition should be suspected if, during the course of the pneumonia, there is an unexplainable rise in temperature, associated with tachycardia, or if the patient is running an unduly protracted course.

It is probable that the etiologic agent responsible for the atypical primary pneumonia is also the cause of the associated pericarditis. Throat cultures, sputum examinations and typing, and blood cultures did not reveal any specific bacterial organisms. Studies were carried out at the Army Medical Museum on blood samples from these patients to ascertain whether the virus of psittacosis, Q fever, or lymphocytic choriomeningitis was present. The results were negative. The presence of a pericardial friction rub in two of these cases and the absence of clinical or roentgenologic evidence of pericardial effusion suggest that the pericarditis was fibrinous in nature. Although in one case the cardiac silhouette, as visualized roentgenographically, did increase in size, its configuration and the symptoms and signs did not suggest pericardial effusion.

Pericarditis is usually secondary to other diseases, particularly pulmonary and cardiac diseases.[5] The pericardium may become involved either by direct extension, by lymphatic or hematogenous spread, or by chemical alterations of the blood. In this group of cases, the roentgenograms of the chest consistently revealed increased bronchovascular markings in the hilar region, radiating to the periphery. Furthermore, the pneumonitis developed on the side in which the bronchovascular markings were increased. In the absence of positive blood cultures and chemical alteration of the blood, it appears that the pericardium became involved secondarily, either by direct extension or by lymphatic spread. All of these patients recovered fully, and, at the time of discharge, there was no clinical, roentgenologic, or electrocardiographic evidence of pericardial disease. Not enough time has elapsed to definitely exclude pericardial adhesions as a complication.

Although the problem of different diagnosis was not difficult in these cases, it is conceivable that at times it would be difficult to rule out rheumatic pericarditis. This is particularly true of rheumatic pericarditis which develops in complete absence of migratory polyarthritis, follows an upper respiratory infection, and is accompanied by signs of pneumonitis. In contrast to the reported cases, the patients with rheumatic pericarditis are more acutely ill, the pneumonitis is evanescent, both clinically and roentgenologically,[6] and a cardiac murmur is usually present. The electrocardiographic changes caused by the pericarditis may be similar in the two diseases, but with rheumatic pericarditis there may be associated alterations in the P waves, prolongation of the P-R interval, and disturbances of rhythm. Patients with rheumatic pericarditis have a more protracted course and require a longer period of rest in bed. Not infrequently they develop permanent endocardial lesions. In one of our cases a harsh systolic murmur developed at the base of the heart during the course of the pericarditis. During convalescence, however, this murmur became less intense and ultimately disappeared. None of our patients developed valvular heart disease. Other types of pericarditis associated with pulmonary disease, such as tuberculous and pyogenic pericarditis, usually do not present any difficulty in differential diagnosis.

All of these patients received short courses of sulfonamide therapy without any apparent benefit. Treatment otherwise was entirely symtomatic, and the disease appeared to run its own course. Rest in bed was maintained until the sedimentation rate and leucocyte count became normal, complete resolution took place in the lungs, and the electrocardiogram returned to normal.

SUMMARY

1. Three cases of pericarditis associated with primary atypical pneumonia are presented.

2. The diagnosis can be made either by the presence of a pericardial friction rub or, more commonly, by typical electrocardiographic changes. It should be suspected if, during the course of the pneumonia, an unexplainable rise in temperature, associated with tachycardia, develops, or if the illness is running an unduly protracted course.

3. The cause of the pericarditis has not been established, but is probably identical with that of the primary atypical pneumonia.

4. Prognosis as to life is good, and, at the end of the hospital stay, no evidence of pericardial disease could be demonstrated.

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Clinical Reports

COR BIATRIATUM TRILOCULARE

CASE REPORT

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COMPLETE absence of the ventricular septum, resulting in the three-chambered heart, is a rare cardiac anomaly. In Abbott's[1] statistical analysis of 1,000 cases of congenital cardiac disease, thirteen cases are reported in which cor-biatriatum triloculare is classified as the primary lesion. In fourteen additional cases, it was found complicating other defects, making the total incidence 2.7 per cent of all that particular series of congenital cardiac abnormalities. The present case report concerns this unusual anomaly occuring as a primary defect.

CASE REPORT

A 9-year-old white boy was admitted to the Massachusetts General Hospital Jan. 26, 1933, because of "heart trouble." His birth was reported as spontaneous at term, and there was no cyanosis. He had always been slightly underweight, but was not a sickly child. He had mumps at the age of 4 years, and measles at 5 years. Both were mild. He had had few sore throats, although his tonsils were said to be enlarged by the school physician. There had been no joint pains or nosebleeds, but he had complained of pain in the calves of his legs that awakened him at night. There was a history of nightmares from which he awakened screaming. His family history was not remarkable except that his father gave a history of rheumatic fever at the age of 16 years, without recurrences.

Two years before entry, a school physician had informed his family that he had heart disease. His mother attempted to limit his activity, but without much success. There was no history of cyanosis on effort or on ordinary exposure to cold, but he did get quite blue when in swimming, even for a short time. He puffed a little more than his siblings when climbing stairs, but had always been very active. He raced and played football and baseball about as well as his playmates. Three weeks before admission, he had a dry cough and diarrhea, and became dyspneic even in a sitting position. There was no swelling of the legs, face, ankles, or hands. His urine was reported as dark, reddish-brown in color for a period of several days, and then appeared cloudy for about one week. On the day of admission. he complained of pain in the right ankle. There was no swelling or redness. His local physi-

cian put him to bed because his heart was enlarged. He had taken tincture of digitalis for nearly three weeks.

Physical examination showed a very ill, pallid boy with shadows and slight puffiness under the eyes and a fine perspiration over the whole body. He had a frequent, hacking cough. The tonsils were moderately enlarged and slightly red, and small cervical lymph nodes were palpable bilaterally. The chest showed marked deformity. There was a bulging asymmetry, with protrusion of the ribs at the costochondral junction on the left, which seemed wider than on the right. There was some flaring of the ribs. A visible, diffuse, heaving impulse was present over the whole left side of the chest, part of the right side of the chest, and in the epigastrium. The left border of cardiac dullness in the fifth intercostal space measured 7½ cm. from the midline, constituting definite cardiac enlargement, and the right border of dullness was also definitely increased. A loud, systolic murmur was heard over the entire precordium and also in the back, but maximally at the cardiac apex. A mid-diastolic murmur was also heard at the apex. An inconstant "friction rub" was heard in the fourth intercostal space about 4 cm. to the left of midsternum. The heart rhythm was regular except for an occasional premature beat. The blood pressure measured 86/68. There was some fullness of the neck vessels. Examination of the lungs revealed some dullness at the left base, behind the heart, in which location a few subcrepitant rales were heard. Larger, moist rales were heard over both bases posteriorly. The liver was palpable four fingerbreadths below the costal margin, and was slightly tender. The spleen was not felt. There were no rheumatic nodules. There was no clubbing of the fingers and little, if any, cyanosis. At the time of admission, the temperature was 99.6° F., the pulse rate, 130, and the respiratory rate, 40.

The laboratory findings were as follows: The initial leucocyte count was 17,650, with 76 per cent polymorphonuclears. The hemoglobin measured 80 per cent (Tallquist). The urine at the time of admission contained many erythrocytes and occasionally leucocytes, but no erythrocytes were found in subsequent specimens. No casts were seen. One blood culture was reported negative. A roentgenogram of the chest, taken on the second hospital day, was reported as follows: "All measurements of the heart are greatly increased. The heart is rounded in shape and there is extreme prominence of the left auricle in both the antero-posterior and oblique views. The hilus shadows show marked increase in density, particularly on the right, extending well out into the lung fields. The periphery of the lung fields is clear. The appearance is consistent with rheumatic heart disease with multiple valve lesions and chronic passive congestion of the lungs. Also consistent with congenital heart disease." (See Fig. 1, A). Ten days later a second roentgenogram was reported as showing no change. However, careful scrutiny does reveal abnormalities of diagnostic importance (Fig. 1, B). The electrocardiogram four days after admission showed sinoauricular tachycardia, a pulse rate of 120, increased voltage, a P-R interval of 0.18 second (somewhat increased for his age), definitely prolonged QRS complexes consistent with intraventricular block, and slight right axis deviation (Fig. 2). No further tracings were made.

Clinical Course.—The temperature remained elevated on the day of admission and rose to 103.8° F. The following day the variation was from 97° to 102° F., and thereafter it varied between 97 and 100.5° F. Treatment consisted of 15 to 30 grains of aspirin daily and supportive

A.
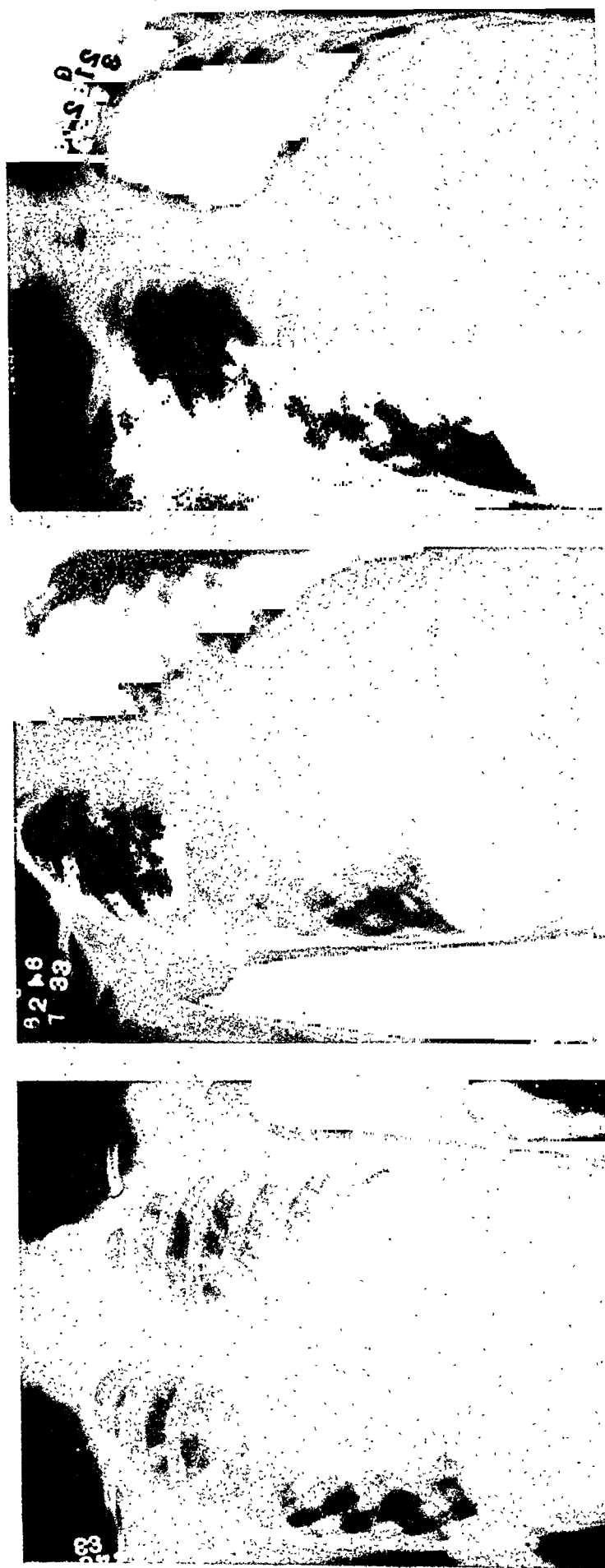
B.

C.

Fig. 1.—A, Taken on the day after admission to hospital. The heart is greatly enlarged in all diameters, and there is extensive pulmonary vascular engorgement. Note the marked density and the width of the supracardiac shadow. B, Twelfth hospital day. Some improvement in the pulmonary vascular congestion. Supracardiac shadow less dense. Note the decreased width of the great vessels and absence of aortic knob. C, Thirty-sixth hospital day, just before death. Cardiac silhouette appears to have increased somewhat in size, and the contour is more bottle-shaped, suggesting pericardial effusion.

measures. For three weeks he showed some improvement. However, orthopnea continued and he found greatest comfort with a high back rest and his knees drawn up. The friction rub heard at the time of admission disappeared. On the seventeenth hospital day, he developed a severe coughing spell and grew more pallid, and, on examination, the heart was found to have increased in size. The leucocyte count at this time was 15,500, and later rose to 28,000 on the thirty-third hospital day. He became gradually worse and began to vomit much of his food.
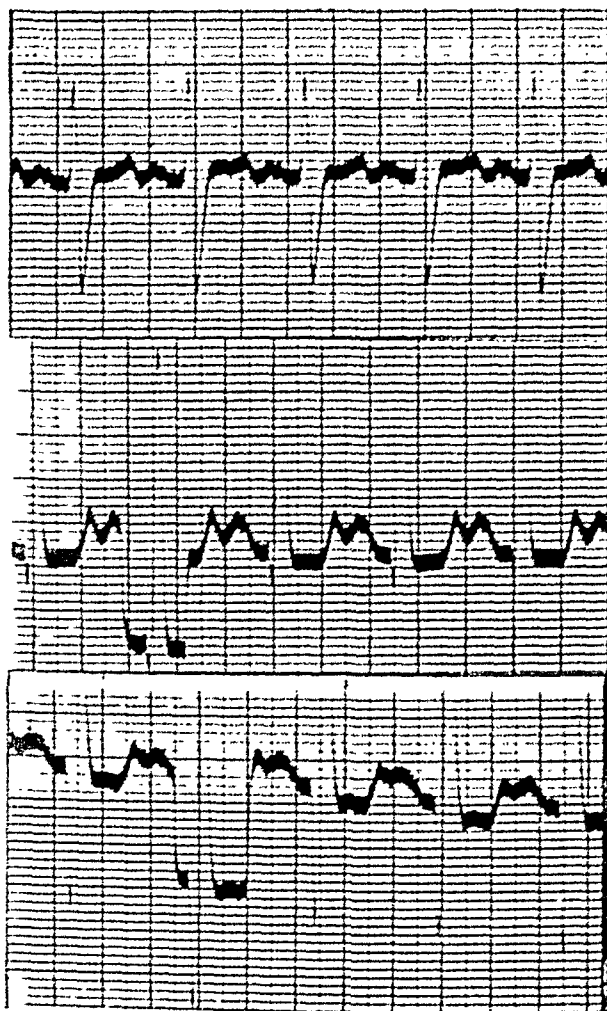
Fig. 2.—Electrocardiogram taken on fifth hospital day. Note sinoauricular tachycardia, pulse rate, 120, slightly prolonged P-R interval (0.18 second), and definite prolongation of intraventricular conduction time (0.12 second), also increased amplitude of QRS complexes. The tendency is to right axis deviation.

Morphine was necessary to induce sleep. The heart appeared to enlarge to such an extent that pericardial effusion was suspected, and, on the thirty-six hospital day, a tap was attempted, but only dark blood was obtained. He died the following morning, March 4, 1933. There was only slight terminal cyanosis. A final roentgenogram of his chest on the day before he died was reported as showing little change except for some evidence of pulmonary atelectasis or fluid at the left base (Fig. 1, C). A clinical diagnosis of acute and chronic rheumatic heart disease, with acute cardiac dilatation and failure, was made.

PERTINENT AUTOPSY OBSERVATIONS

Autopsy revealed a well-developed and well-nourished boy of 9 years, weighing about 70 pounds. who showed a bulging precordium with four puncture marks in the skin. The liver was enlarged, and lay entirely below the costal margin. The two halves of the diaphragm were at the eighth rib. There was partial collapse of both lungs, but no pneumonia was seen. The pericardium was filled with 750 c.c. of unclotted blood. The heart was estimated to weigh about 600 grams. At the apex of the heart, on its anterior surface, two small puncture wounds were seen,
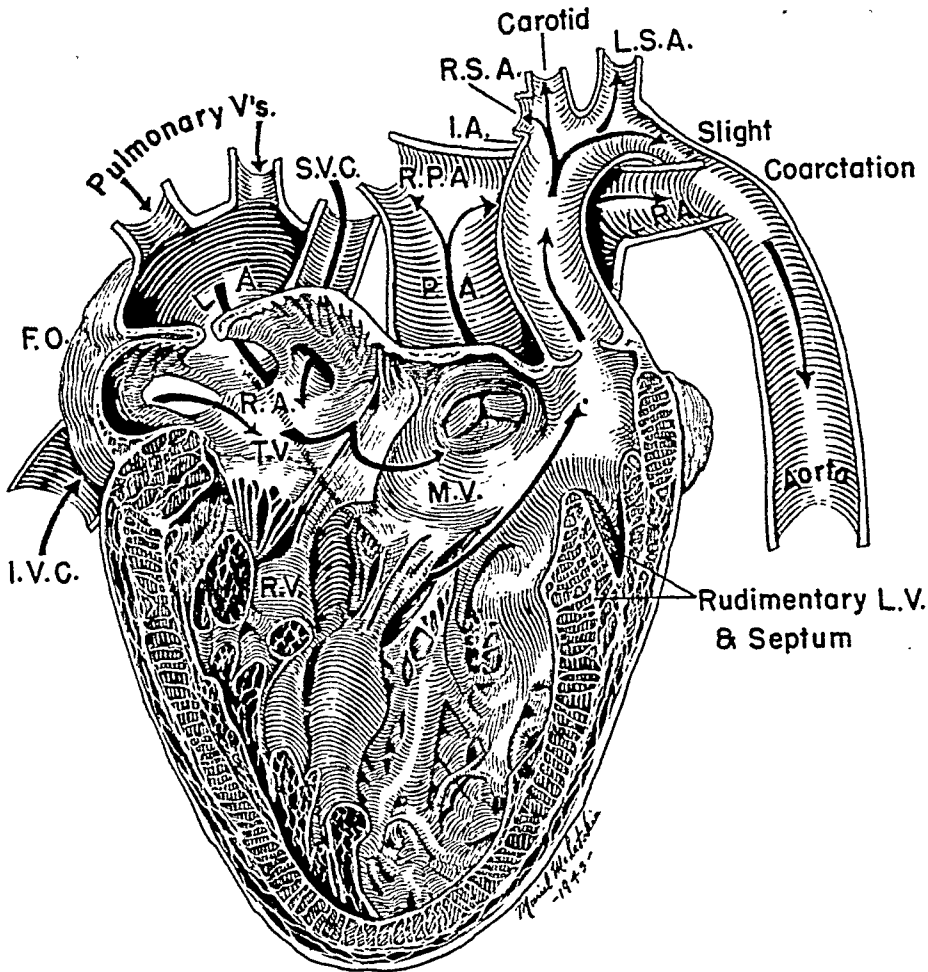
Fig. 3.—Schematic drawing of heart, laid open, showing large, common (right) ventricle and small rudimentary left ventricle. Note relatively small, coarctated aorta and large dilated pulmonary artery. *M.V.*—mitral valve, *T.V.*—tricuspid valve, *R.A.*—right auricle, *I.V.C.*—inferior vena cava, *F.O.*—foramen ovale (patent), *L.A.*—left auricle, *S.V.C.*—superior vena cava, *P.A.*—pulmonary artery. *R.P. A.*—right pulmonary artery, *L.P.A.*—left pulmonary artery, *I.A.*—innominate artery, *L.S.A.*—left subclavian artery.

around which there was a small amount of fibrin and hemorrhage into the muscle. Two other puncture wounds were found in the region of the right auricular appendage, covered by a recent, adherent, greyish-red, ante-mortem thrombus. The heart was very large, and the ventricular wall measured 22 mm. in thickness. The superior and inferior venae cavae entered the right auricle in normal fashion, and a patent foramen ovale, 1 cm. in diameter, was present. The left auricle received the pulmonary veins normally. There was one large ventricular cavity, with a very small outpocketing which doubtless represented the rudimentary left ventricle or bulbus. From the large ventricular cavity

the aorta arose at the anterior upper left margin. The base of the aorta formed the definite bulb just mentioned. This bulb was seen to be made up of a small chamber about 3 cm. in diameter, partially separated by a ridge of tissue (rudimentary septum) from the large, essentially common ventricle (Fig. 3). The aorta measured 2 cm. in diameter at its site of origin. The relationship of the pulmonary artery to the aorta was that which would be present in a normal heart if it failed to rotate to the left. The valves were not opened and measured, but, on inspection, all but the mitral valve seemed smooth and competent. The mitral valve was thickened along its free border, but no vegetations were present. The coronary arteries were normal in origin. The diameter of the dilated pulmonary artery was several times that of the aorta. Just past the site of origin of the left subclavian artery, the aorta was slightly to moderately coarctated, and measured 8 mm. in diameter at this point. Also at this point, the aorta appeared to take an angular bend, and became the descending aorta, measuring 1.8 cm. in diameter. The ductus arteriosus left a small dimple in both the pulmonary artery and the aorta. It measured 8 mm. in diameter, and, on cut section, a pin-point lumen remained. The anatomic diagnoses were as follows: Cor biatriatum triloculare, with rudimentary left ventricle; cardiac hypertrophy and dilatation; congestive heart failure; patent foramen ovale; slight coarctation of the aorta; puncture wounds of the heart; hemopericardium; and pulmonary congestion and atelectasis.

<div align="center">DISCUSSION</div>

The clinical features of this case are unusual. Congenital cardiovascular defects with this degree of venoarterial communication are, with few exceptions, attended by at least a moderate degree of cyanosis, which was not clearly present in this patient even in his final illness. The fact that physical disability among congenital cardiacs may be more or less directly proportional to the degree of cyanosis most probably explains the history concerning his physical activity. Nevertheless, despite the benign early history, he survived only by one year, or so, the mean age (7¾ years), as given by Abbott[1] in thirteen cases of this malady.

Consideration of the pathologic anatomy suggests an explanation for the absence of cyanosis. First, the location of the aorta was such that the arterial blood returning via the mitral valve doubtless formed a barrier against too great admixture with venous blood returning via the tricuspid valve, as is apparently the case in the three-chambered turtle's heart. If this assumption is correct, the blood leaving the heart through the aorta must have been very predominantly arterial. Secondly, the great size of the pulmonary artery, as compared to the aorta, served the process of oxygenation of the blood well until dilatation and failure of the heart made this no longer possible. The part played by coarctation of the aorta in bringing about the final break is problematical; it does not seem likely that it was of any real importance. No blood pressure readings were made prior to his hospital entry, and those made after admission did not suggest coarctation. Also, no characteristic notching of the ribs was seen in the chest roentgenograms.

Each observer who saw this patient concurred in the diagnosis of rheumatic heart disease with mitral involvement, and interpreted the febrile illness as an active rheumatic infection, which indeed it may have been, although no microscopic evidence of this was found in the myocardium. The presumably acquired heart disease discovered at the age of 7 years, the joint pain, fever, leucocytosis, enlarged heart, murmurs, precordial friction rub, and later the apparently enlarging cardiac silhouette, suggesting pericardial effusion, altogether favored this conclusion. In reviewing the available objective clinical evidence there are two important indications of congenital heart disease that were overlooked, namely, the delay in intraventricular conduction time, and extensive excursions of the QRS waves, as shown by the electrocardiogram (Fig. 2), and the definitely abnormal supracardiac (aortic) shadow in the roentgenogram (Fig. 1). The reasons for both were at once apparent at the post-mortem table. There was no septum to carry the bundle branches in a normal fashion, and the aorta was hypoplastic and abnormally situated. In view of our present knowledge, the apical systolic and diastolic murmurs were most likely produced by a dilated (insufficient), relatively stenotic, mitral ring opening into a markedly dilated ventricular cavity. It is unlikely that the loud, widely transmitted systolic murmur arose from the site of slight coarctation in the aorta. The unfortunate result of the attempted pericardial taps re-emphasizes the difficulty that sometimes attends the differential diagnosis of pericardial effusion and cardiac dilatation, and illustrates the possible danger of paracentesis in this region. Whatever pericardial effusion may have been present was obscured at autopsy by the extensive hemopericardium.

SUMMARY

A case of three-chambered heart (cor biatriatum triloculare), with a tiny, rudimentary left ventricular pocket, attended by slight coarctation of the aorta in a boy aged 9 years is reported. The unusual clinical features, namely, absence of cyanosis and relatively good cardiac reserve until shortly before death, are discussed. The congenital abnormalities were complicated by a terminal infection (? rheumatic) and rapid dilatation and failure of the heart. The clinical diagnosis of chronic rheumatic heart disease, with mitral involvement was incorrect.

REFERENCE

1. Abbott, Maude E.: Atlas of Congenital Cardiac Disease, New York, 1936, Am. Heart Assoc.

Abstracts and Reviews

Selected Abstracts

Green, H. D., Lewis, R. N., Nickerson, N. D., and Heller, A. L.: Blood Flow, Peripheral Resistance, and Vascular Tonus, With Observations on the Relationship Between Blood Flow and Cutaneous Temperature. Am. J. Physiol. 141: 518, 1944.

Vascular tonus is defined as the active contraction of the muscular walls of the small blood vessels and is considered to be influenced, physiologically, by vasomotor nerve impulses, humoral substances, and metabolic products. The summated effects of the first two are defined as the vasomotor activity. Changes in vascular lumen in response to altered intraluminal pressure, per se, are considered to be a physical reaction and not to represent a change in vascular tonus.

The relationship between vasomotor activity, peripheral resistance, blood flow, and subcutaneous temperature was studied by recording either the arterial inflow or the venous outflow at a series of perfusion pressures in various vascular beds in the hind limbs of anesthetized dogs. These studies were made during control states, during periods of increased vasomotor activity occurring spontaneously and induced by small hemorrhages, and during periods of decreased vasomotor activity induced by sectioning the sciatic nerve. Average blood flow, at mean arterial pressure, was 6.9 ml. per 100 Gm. of muscle. In the combined skin and muscle of the lower half of the hind extremity, the average flow was 3.2 ml. per 100 grams of extremity, and, in the skin of the latter, the average flow was 1.6 ml. per 100 grams of extremity.

Only experiments in which the hematocrit reading and viscosity of the blood remained within +4 to −6 per cent of the control values and in which collateral circulation artifacts were avoided were analyzed. During a constant state of vasomotor activity the increments of blood flow per increment of perfusion pressure in skin and often in muscle increased regularly from zero upward when flow was measured immediately after establishment of the perfusion pressure. The relationship between perfusion pressure and flow in these experiments could be represented by the equation $F = \dfrac{P^n}{C}$, where n has values between 1 and 5, usually about 2. This relationship appears to be explainable on a purely physical basis. When the rate of flow was measured one to two minutes after establishment of the perfusion pressure in muscle and in the whole distal part of the extremity, the flows at pressure below mean arterial pressure appeared to be relatively greater than they would be on the basis of a purely physical relationship between pressure and flow. This was probably due to a vasodilatation induced locally by the accumulation of metabolic products as a result of the slowed flow at low perfusion pressures, but might also be due to a lowering of the extravascular pressure. The result was a sigmoid rather than a parabolic shaped curve relating perfusion pressure and flow.

In all experiments, increase of vasomotor activity decreased the rate of flow at each perfusion pressure. In those experiments in which the data fitted the equation $F = \dfrac{P^n}{C}$, increase of vasomotor activity increased the magnitude of the constant C and of the exponent n.

Peripheral resistance, physically, is the ratio of the perfusion pressure to the flow through the vascular bed. The term *PRU* is proposed as a unit of peripheral resistance, where $1 \text{ PRU} = \dfrac{1 \text{ mm.Hg}}{1 \text{ ml./min.}}$. Peripheral resistance was found to be altered when the perfusion pressure was raised or lowered, even when vasomotor activity remained constant. Conversely, change of vasomotor activity was not, in all cases, correctly indicated by an appropriate alteration of peripheral resistance.

Various methods of expressing change of vasomotor activity were discussed. It was concluded that the only completely satisfactory method is to compare the plot relating pressure to flow over the complete range of pressures from zero to mean aortic pressure in a control period, with a similar plot obtained in the experimental period. However, this method is laborious, and it is difficult to depict the progressive changes in these plots with time. As a compromise the next most satisfactory method appears to be to determine, during a control period, the relationship between pressure and flow over the entire range of flows anticipated during the subsequent experimental period, and thereafter to make only single determinations of pressure and flow, usually at a perfusion pressure equal to the existing mean aortic pressure. The results may then be expressed in terms of the ratio of the peripheral resistance (or perfusion pressure) in the experimental period to the peripheral resistance (or perfusion pressure) observed during the control period at the same rate of flow.

<div align="right">AUTHORS.</div>

Corcoran, A. C., Taylor, R. D., and Page, I. H.: **Immediate Effects on Renal Function of the Onset of Shock Due to Partially Occluding Limb Tourniquets.** Ann. Surg. 118: 871, 1943.

The depression of renal function during the onset of shock due to partially occluding tourniquets is due to a decrease of renal blood flow, which is only in a minor and inconstant measure the result of decreased arterial pressure.

This decrease of renal blood flow is due, almost wholly, to increased renal vascular resistance, in which increased blood viscosity enters only in a small degree; the increased resistance being rather due to vasoconstriction, predominantly affecting the glomerular efferent arterioles.

Although nervous stimulation, presumably as the result of pain, causes a small measure of this vasoconstriction, the larger fraction is independent of the renal nerves and, by exclusion, of humoral origin.

This humorally-arising renal vasoconstriction is associated with the appearance of a vasoconstrictor substance in plasma, to the activity of which it is therefore attributed.

<div align="right">AUTHORS.</div>

McMichael, J., and Sharpey-Schafer, E. P.: **Cardiac Output in Man by a Direct Fick Method.** Brit. Heart J. 6: 33, 1944.

Serial estimations of cardiac output and right auricular pressure can be made by means of a ureteric catheter passed along the veins into the right auricle.

Normal resting values for arteriovenous oxygen differences were rather lower than those obtained previously by the acetylene method.

Cardiac output in the supine posture showed a 33 per cent increase over that in the erect.

A fall in right auricular pressure reduced, and a rise in right auricular pressure increased, the cardiac output.

Acceleration of the heart with atropine usually increased cardiac output and caused a fall in right auricular pressure. Occasionally the fall in right auricular pressure may operate against an increase in cardiac output.

Intravenous adrenalin, in doses that did not accelerate the heart or raise the blood pressure increased cardiac output.

Normal subjects with high resting outputs had faster heart rates than the others.

AUTHORS.

Dawson, G. D., and Jones, A. M.: Synchronous Heart Sound Recordings. Brit. Heart J. 6: 48, 1944.

A method of synchronous heart sound recording is described in which the standard Cossor-Robertson cardiograph is modified by introducing a second channel, using the Clothier electronic switch.

Synchronization of the tracings is automatic and requires no adjustment.

The alteration to the commercial instrument is simple and does not affect its use as a simple portable cardiograph.

AUTHORS.

Stern, V. S.: Stokes-Adams Attacks in a Child. Brit. Heart J. 6: 66, 1944.

A case of insidious rheumatic pericardial effusion with Stokes-Adams attacks is described. A boy of 12 years sought medical help after three months of ill health, and only when disturbance of the conducting system had set in. Either minor inflammation of the bundle tissue itself or its compression by inflammatory vascularization of the collagenous mass in the septum membranaceum, would explain the symptoms.

AUTHOR.

Campbell, M.: Complete Heart Block. Brit. Heart J. 6: 69, 1944.

Complete heart block is most often seen in men in the seventh decade with enlarged hearts and atherosclerosis but no other evidence of gross heart disease. Four-fifths of our patients were men. Most (45 per cent) were between 60 and 69 years of age, and 84 per cent were over 50 years of age at the onset of complete block.

Syphilitic and rheumatic heart diseases were, between them, responsible for only a little over 10 per cent of the cases. Other myocardial disease was responsible in 75 per cent, or in 86 per cent if the group of congenital cases was excluded, this being the second commonest cause (13 per cent). Cardiac enlargement with no other signs than atherosclerosis of the aorta and often of peripheral arteries was the evidence of myocardial disease in nearly half these cases, high blood pressure, angina pectoris, or congestive failure being present in the other half. In the ten cases with high blood pressure, the average figure was 225/108. In the others, the systolic pressure was above and below 160 in equal numbers, and the average figures for these two groups were 194/81 and 137/73. Thus, in the latter, the pulse pressure was only slightly raised, but in the former and in those with high blood pressure, the pulse pressure averaged 115. The reasons for this have been discussed.

The heart rate was usually between 28 and 40 and averaged just under 35 (excluding congenital cases where it was generally 40 to 56).

Heart block may be of very varied types; it may be: (1) complete, (2) partial; 2:1, or more rarely 3:1 or 4:1, (3) partial with dropped beats only; including regular 4:3, 3:2, etc., or occasional dropped beats, or (4) latent, with a prolonged P-R interval only.

Complete heart block is a serious lesion, though some patients, especially some of those under 40 years of age, live for many years in reasonably good health. There were 50 cases followed for more than 2 years or until their death; 34 were

dead after an average period of 2.5 years; 16 were alive after an average period of 6 years or 4.5 years if two exceptional cases were excluded. Of the former, 19 died in less than 2 years, 14 in from 2 to 6 years, and 1 after 12 years. Of the latter, the period of observation was from 2 to 6 years in 10, and from 7 to 20 years in the other 6 cases.

Stokes-Adams attacks were present in half the patients with complete heart block. When they were present they were one of the earliest if not the first significant symptom of heart block in three-fourths of the cases. In those without Stokes-Adams attacks, dyspnea or attacks of faintness or dizziness were the main presenting symptoms.

Stokes-Adams attacks were no more common in those who had *recorded* latent heart block than in those without. A known change of rhythm at times other than those of the attack does makes Stokes-Adams more likely, but not as much as might be expected (64 against 32 per cent).

The prognosis was considerably worse in those with Stokes-Adams attacks, the results in the patients traced being:

	Alive	Dead
With Stokes-Adams attacks	6	24
Without Stokes-Adams attacks	10	10

The method of dying was even more strikingly different: of the patients with Stokes-Adams attacks, 61 per cent died suddenly, presumably in attacks; of those without Stokes-Adams attacks, only one was known to have died suddenly, and 50 per cent died with failure. If, when a patient is first seen with complete heart block, he has not had a Stokes-Adams attack, the risk of such an attack developing, or of his dying suddenly, is not great, and with each month that has passed the risk becomes still less.

It is important to realize that Stokes-Adams attacks may occur with paroxysmal heart blocks (complete) and the paroxysms may be of short duration after the attacks and may easily be missed. Otherwise attacks that are true Stokes-Adams attacks will remain unexplained.

AUTHOR.

Cossio, P., and Berconsky, I.: The First Heart Sound and Auricular Fibrillation. Rev. argent. de cardiol. 10: 283, 1943.

The heart sounds were studied by auscultation and graphic records in five patients during periods of auricular fibrillation and sinus rhythm. It was found that, when auricular fibrillation was present, the first sound was of greater intensity and appeared later in relation to the beginning of the QRS group of the electrocardiogram.

The greater intensity of the first heart sound during auricular fibrillation is explained if due consideration is given to the origin of the first sound, fundamentally valvular, and to the preponderance role of the initial tension of the A-V valves in determining its intensity.

AUTHORS.

Thomas, C. B.: The Significance of Electrocardiographic Abnormalities in Young Adults. Bull. Johns Hopkins Hosp. 74: 229, 1944.

There are a number of physiologic mechanisms which may alter the electrocardiogram, sometimes to an abnormal degree. In the age groups in which degenerative disease of the myocardium is rare, there is greater likelihood that a given electrocardiographic abnormality is a physiologic variant than evidence of a pathologic lesion. Until the limits of normal variation in the human electro-

cardiogram have been much more thoroughly explored, the diagnosis of heart disease in young persons should seldom be based on the electrocardiographic findings alone, in the absence of clinical manifestations.

AUTHOR.

Zimmerman, S. L.: Transient T-Wave Inversion Following Paroxysmal Tachycardia. J. Lab. & Clin. Med. 29: 598, 1944.

One case of supraventricular tachycardia and two cases of ventricular tachycardia followed by T-wave inversion in multiple leads, persisting for a variable period of time and not associated with myocardial infarction, are presented.

The importance of correct evaluation of these changes is stressed.

The role that quinidine played is discussed. It does not appear to have been of etiological importance.

Certain differential electrocardiographic findings are discussed, and their importance in excluding myocardial infarction is stressed.

Persistent inversions of T waves following tachycardias are not necessarily of ominous prognostic import.

AUTHOR.

Davies, J. N. P., and Fisher, J. A.: Coarctation of the Aorta, Double Mitral A-V Orifice, and Leaking Cerebral Aneurysm. Brit. Heart J. 5: 197, 1943.

The case is reported of a male, aged 17 years, with coarctation of the aorta and other congenital defects. He developed a cerebral hemorrhage from a berry aneurysm, and made a complete recovery from this, only to die later from a rupture of the aorta.

The autopsy revealed that, in addition to the coarctation of the aorta and associated defects of elastic tissue, there was a double mitral valve. The probable counterpart during life of this rare anomaly was a presystolic or diastolic murmur in the mitral area.

The relationship of these defects is briefly discussed.

AUTHORS

Baer, S., and Frankel, H.: Studies in Acute Myocardial Infarction. III. Diagnosis and Location of the Infarct by Electrocardiogram. Arch. Int. Med. 73: 286, 1944.

The diagnosis and location of the infarct were considered in 378 cases of acute myocardial infarctation. Electrocardiograms taken in 321 cases revealed the presence of infarction in 94 per cent. On electrocardiographic study alone, 52 per cent of the infarcts were found to be anterior and 34 per cent posterior. Of 74 patients coming to necropsy, 70 per cent had anterior, 23 per cent posterior, and 7 per cent anteroposterior infarction.

Anterior myocardial infarctions are more frequent and more serious than posterior infarctions. Infarction of the anterior wall of the left ventricle is more apt to be missed by electrocardiograms than posterior involvement. Electrocardiographic diagnosis and location of the infarction are highly accurate.

AUTHORS.

McHardy, G., and Browns, D. C.: Life Expectancy After an Attack of Myocardial Infarction. Report of a Case of Survival for Nineteen Years After Coronary Thrombosis. Arch. Int. Med. 73: 290, 1944.

The authors report the present case as the first instance of myocardial infarction due to coronary thrombosis in which there was electrocardiographic confirmation at the onset, and in which the patient lived for so long a time—nineteen

years and thirty days from the initial occlusion until his death, from thrombosis. Both the initial and the terminal attack were confirmed by autopsy.

AUTHORS.

Harrison, T. R.: Clinical Aspects of Pain in the Chest. I. Angina Pectoris. Am. J. M. Sc. 207: 561, 1944.

An analysis of seventy-seven patients with angina pectoris has been made, with particular reference to the characteristics of the pain and its relationship to various body functions.

The pain was felt in the substernal *location* in only about one-half the patients. Pain entirely limited to the periapical, axillary, or abdominal regions did not occur in any case.

The *duration* of the pain was usually a few minutes only, rarely longer than one-half hour. No patient had pain lasting for a few seconds only.

Pain of great *intensity* was exceptional, the discomfort being mild or minimal in more than one-half the patients.

The discomfort was constrictive or heavy in *character* in only about 50 per cent of the cases. Frequently, the pain was of an aching quality; burning discomfort was occasionally found; while lancinating pain was encountered in only one subject.

In addition to the generally recognized "trigger" factors of exertion, eating, emotion, and cold, the recumbent posture and glucose deficiency were found to be common precipitating causes of the seizures. Anginal attacks with typical electrocardiographic changes may be induced by spontaneous hypoglycemia in patients who have no seizures with severe effort and no evidence of structural cardiac disease. The act of eating may precipitate anginal attacks in certain patients and may prevent the attacks in other subjects.

Pain induced by the sitting or standing position or aggravated by breathing, coughing, or swallowing can usually be safely ascribed to disorders other than angina pectoris.

In the diagnosis of angina pectoris the most important features are: the history of relationship to effort, the short duration of the pain, and the demonstration that the amount of muscular effort required to induce the pain is increased by nitroglycerin.

A large percentage of patients with angina pectoris also suffer from chest pain due to other disorders. Such disorders may either be related to angina pectoris (as in the case of myocardial infarction and reflex disturbances of the skeletal system) or unrelated to it (as in the case of gall bladder disease, hiatal hernia, esophageal spasm, and so forth). Because of the frequent coexistence of the two causes of chest pain, one of them may be overlooked unless unusual care is employed in obtaining the history.

Occasional patients—about 10 per cent in this series—may have anginal attacks which have never been related to effort. Among the causes of such attacks are status anginosus ("coronary insufficiency," "preinfarction angina") ectopic tachycardia, spontaneous hypoglycemia, and conditions such as intermittent claudication, congestive failure, and undue anxiety about the cardiac condition, which induce the patient to lead an unusually sedentary life. It is in this group of patients that the greatest diagnostic difficulty is likely to be encountered.

AUTHOR.

Dodge, K. G., Baldwin, J. S., and Weber, M. W.: The Prophylactic Use of Sulfanilamide in Children With Inactive Rheumatic Fever. J. Pediat. 24: 483, 1944.

Eighty-eight children and adolescents with quiescent rheumatic disease were given from 1 to 2 Gm. of sulfanilamide daily throughout the winter and spring months for a total of 181 patient-seasons.

One hundred and one rheumatic children were observed as controls for 138 patient-seasons.

In the group receiving sulfanilamide, in some cases for as many as four seasons, toxic drug reactions were minimal. The drug was not discontinued permanently in any case for such a reaction.

During the period of the study, there were, in the control group, fifty-four Group A hemolytic streptococcal infections, an incidence of 39 per cent. There were nineteen definite major rheumatic relapses (with two deaths) and seven mild or possible relapses. In three children, the rheumatic process remained active throughout the period of observation, and there was one death from subacute bacterial endocarditis.

In contrast to this, only five hemolytic streptococcal infections occurred in the group of children receiving sulfanilamide prophylaxis, an incidence of 2.7 per cent. Two children, or 1.1 per cent of the patient-seasons of prophylaxis, developed definite rheumatic relapses while taking the drug regularly. Two other children with severely damaged hearts died of congestive failure without evidence of streptococcal infection or active rheumatic disease. Two children with recently active rheumatic fever showed signs of increasing rheumatic activity within two weeks of starting the drug. The remainder of this group of children remained free of streptococcal infection and rheumatic relapses.

Some of the problems of the administration of a sulfonamide prophylactically have been discussed.

Based on this study and reports in the literature, the effectiveness of sulfonamide prophylaxis in quiescent rheumatic fever is established, and it should be applied more widely among groups of highly susceptible individuals.

AUTHORS.

Davis, D. B., and Rosin, S.: Rheumatic Fever and Rheumatic Heart Disease in Los Angeles Children. J. Pediat. 24: 562, 1944.

The cases of 157 patients with childhood rheumatic disease admitted to the Los Angeles County Hospital over a five-year period are analyzed and discussed. The following salient findings bear emphasis:

The relatively low incidence of rheumatic disease, as determined by this survey, is consistent with the findings of similar studies carried out in other cities with subtropical climates.

Chorea seems to occur with much less frequency in this area than in eastern population centers.

No significant variation in seasonal incidence is noted.

An analysis of temperature, rainfall, and relative humidity permits no correlation between these factors and the incidence of the disease in this area.

Familial incidence in this series is negligible.

Two-thirds of the patients were born and raised in this community. Almost 80 per cent of those born out of California lived in the Los Angeles areas over one year before the onset of rheumatic disease. These facts would certainly tend to discredit the commonly held belief that the majority of the patients with rheumatic infection encountered here are migrants from eastern or northern states.

The mortality in this series was 9.5 per cent. Brief summaries are presented of all cases that proved fatal.

AUTHORS.

Thompson, R. B.: A Case of Myxoma of the Left Auricle. Brit. Heart J. 6: 23, 1944.

A case of myxoma of the left auricle with congestive heart failure and sudden death is presented with an autopsy report.

AUTHOR.

Evans, W.: The Heart in Myotonia Atropica. Brit. Heart J. 6: 41, 1944.

Examination of the heart in thirteen cases of myotonia atrophica has shown that the presence of cardiovascular signs may help in the earlier diagnosis of the condition.

The pulse is often small and occasionally infrequent. The blood pressure is sometimes very low. The first heart sound in the mitral area commonly shows splitting, and sometimes triple rhythm may appear from addition of the fourth heart sound, this depending on the degree of elongation of the P-R period.

The changes that commonly characterize the electrocardiogram include elongation of the P-R period, low voltage of the P wave, slurring of the QRS complex, and left axis deviation.

The size of the heart varies so that it may be normal or may appear small, but in the presence of considerable lengthening of the P-R period, moderate enlargement takes place.

AUTHOR.

Pietrafesa, E. R.: Observations on Two Cases of Arteriovenous Communication. Rev. argent. de cardiol. 10: 302, 1943.

A study was made of the circulatory changes which appeared in two patients with an arteriovenous aneurysm of the right leg, when the femoral artery was compressed at the level of the Poupart's ligament. The heart rate, the oscillatory index of the limb arteries, the different phases of the cardiac cycle, arterial and venous pressure, cardiac output, heart size, electrocardoigram, and heart sounds were investigated.

It is concluded that the circulatory changes produced by compressing the artery of an arteriovenous aneurysm are not always the same. The size of the arteriovenous fistula, the time of its establishment and the circulatory compensation which follows are among the factors which determine the circulatory response to compression of the artery.

AUTHOR.

Langley, G. F.: Repair of Ruptured Popliteal Artery, With Note on Heparin Therapy After Arterial Suture. Brit. J. Surg. 31: 161, 1943.

A case of rifle bullet wound of the popliteal vein with delayed rupture of the popliteal artery has been described. Suture of the popliteal artery after rupture of an arterial hematoma was successfully performed. External, popliteal nerve palsy developed as a secondary complication, but the patient recovered from this.

Heparin administration probably contributed to the saving of the limb. It is suggested that heparin should be administered in a continuous saline drip, as it is unlikely to be effective by intermittent intravenous injection; the accepted dosage of heparin may be too small, and it is necessary for repeated examinations of the clotting time to be made.

AUTHOR.

Bloom, N., and Walker, H.: Nodal Rhythm and Bundle Branch Following Aspirin Hypersensitivity. J. Lab. & Clin. Med. 29: 595, 1944.

Aspirin is an excellent analgesic and, considering its enormous consumption, only occasionally causes any severe reactions in human beings. This case is an example of very unusual sensitivity to the drug. Anaphylactic shock with transient nodal rhythm and bundle branch block occurred after the ingestion of five grains of aspirin. Within twenty-four hours, all of these phenomena had disappeared.

AUTHORS.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

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The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

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Executive Committee.

Original Communications

THIOCYANATE THERAPY OF HYPERTENSION

Studies on the Constancy of Blood Concentration and Urinary Output

Arnold Koffler, M.D., A. W. Freireich, M.D., and
Major I. Jerome Silverman, M.C., Army of the United States

THIOCYANATE was originally studied pharmacologically by Bernard,[1] in 1857, but it was first applied as a therapeutic agent by Nichols,[2] in 1925. There then followed a group of sanguine reports of its efficacy as an agent in the control of high blood pressure, as exemplified by the studies of Gager,[4] Smith and Rudolf,[5] Bolotin,[6] Maguire,[7] and Palmer, Silver, and White.[8]

This buoyant period was followed by a series of reports of toxic effects by such writers as Ayman,[9] Palmer and Sprague,[10] and Goldring and Chasis.[11] With the introduction, in 1936, by Barker,[3] of a method of controlling the dosage of the drug by means of blood concentration estimations, we have arrived at a sane, middle-of-the-road policy. We are now better able to evaluate the drug, ascertain its efficiency, and control the dosage. That toxicity was caused by lack of control of the dosage is evidenced by the reports of O'Hare and his associates.[12] In 1931, before the introduction of Barker's method for ascertaining the blood level of the thiocyanates, and using empirical doses, these authors reported favorable results in only two out of twenty-five cases. Moreover, "every patient complained of one or more distressing symptoms arising from two to eight days after the drug was commenced." A study of the amount of thiocyanate used in their cases in the light of present knowledge readily explains the rapid onset of toxic symptoms. They gave their patients 1 Gm. daily for one week, then 0.6 Gm. daily for one week, and, finally, 0.3 Gm. daily. In the majority of patients such an early heroic dose will yield blood levels of 20 mg. per 100 c.c. or more, and naturally will bring them, in two to eight days, to a period

of toxicity. As we shall demonstrate, as little as 0.1 Gm. daily may be sufficient in some cases to maintain a therapeutic blood level.

In 1938, using Barker's method of control, O'Hare and his associates[13] again tried the drug on fifteen patients. This time they reported that "in all cases a definite lowering of the blood pressure occurred during the interval of treatment." They found that the symptoms returned when the drug was surreptitiously omitted, and concluded: "the regulation of administration required the individualization of dosage for each patient, frequent blood cyanate determinations, and sufficient intelligence on the part of the patient to permit an awareness of early toxic symptoms."

The truth, as would be expected, lay in the fact that a very important element in the therapeusis had been overlooked; namely, failure to evaluate the results on the basis of the amount of drug available for action in the circulating blood, rather than the dosage prescribed. This fact was clarified by the work of Barker in his original report in 1936[3] and in his subsequent writings.[14-16, 26] Many other workers[17-24] have confirmed his results, so that now it is pretty well conceded that no therapeutic effect with thiocyanate can be truthfully judged without adequate blood level determinations at fairly frequent intervals. A study of the unfavorable reports reveals that the toxic manifestations and fatalities were most probably caused by excessive dosage. These unfortunate sequelae may very well have been averted by a proper determination of the blood level, for the dosage, per se, is no indication of the amount of the drug available in the circulating blood. On the contrary, the full therapeutic effect may be obtained with a very small dose in one case, whereas many times the same amount of drug may be required for another.

CLINICAL RESULTS

We have adequately followed thirty-nine ambulatory patients in our clinic during the past three years. The patients had essential hypertension, and many of them showed some evidence of cardiac or renal complication. There were seventeen males and twenty-two females, and their ages ranged from 34 to 71 years; the average age was 55 years.

The method employed was as follows: All of these patients had been observed for months, and many for years, with the usual therapeutic agents, so that the base level of their blood pressures was known. After the period of observation, potassium thiocyanate therapy was instituted. We used an aqueous solution of the drug in such concentration that one dram contained 0.1 Gm., and commenced with a dose of one dram three times daily. After one week the patient was examined, the blood pressure recorded, and a blood specimen was obtained. All blood pressures were taken in the recumbent posture, and after the patient had rested for at least ten minutes in that position. Many of the observations were checked by more than one physician. Since ours is an ambulatory cardiac clinic, held only once weekly, and the thiocyanate determination could not be performed immediately, the dose was maintained and the

patient was told to report the following week, at which time the dose was adjusted according to the blood level. Although in most patients the average blood level with this dose (0.1 Gm. three times daily) was 5 mg. per 100 c.c., as high a level as 15 mg. per 100 c.c. was obtained with this small amount. In those cases in which there were signs of congestive heart failure, digitalis therapy and diuretics were continued. Such a regime was not incompatible with the thiocyanate.

The following five cases were selected as typical examples of both the favorable and unfavorable results:

CASE 1.—(Fig. 1.)   M. K., a woman, aged 48 years. was first admitted to the cardiac clinic May 31, 1938, with a diagnosis of (a) hypertension, (b) enlarged heart, (c) regular sinus rhythm, (d) Class III C. Her chief complaints were dyspnea, cough, palpitation, precordial pain, edema of the ankles, fatigue, pallor, and cyanosis. The blood pressure on admission was 240/130. A teleoroentgenogram revealed that the heart was enlarged in all diameters. There were straightening of the left cardiac border and accentuation of the right auricular curve. The aorta was not dilated. In addition, there was roentgenologic evidence of fibroid changes at the roots and bases of both lungs, especially on the right side. There was no pleural effusion. The electrocardiogram revealed a rapid sinus rhythm, with deviation of the electrical axis to the right. Numerous urine examinations showed a good ability to concentrate; the specific gravity ranged from 1.002 to 1.027, and there were no abnormal elements. The nonprotein nitrogen of the blood was 35 mg. per 100 c.c., and the glucose, 84 mg. per 100 c.c. The hemoglobin was 98 per cent, the erythrocyte count, 4 million per cu. mm., and the leucocyte count, 11,700 per cu. mm., with 70 per cent polymorphonuclear cells, 24 per cent lymphocytes, and 6 per cent transitionals. The blood Wassermann reaction was negative.

She was treated with phenobarbital, digitalis as indicated, and numerous expectorant mixtures for the chronic cough. During this period she showed persistent hypertension, with the systolic pressure between 190 and 240, and the diastolic between 116 and 140.

Potassium thiocyanate therapy was instituted after an observation period of ten months. The initial dose was 0.1 Gm. three times daily. One week later the blood pressure was still elevated, there was no change in her symptoms, and a blood thiocyanate determination showed 3.6 mg. per 100 c.c. The dose was increased to 0.2 Gm. three times daily, and, a week later, the blood pressure had fallen to 172/104 and the blood thiocyanate was at a level of 13.3 mg. per 100 c.c. There were no toxic symptoms, and the patient felt considerably improved, so the dose was continued at 0.2 Gm. three times a day. The next week she began to have dizziness; the blood pressure had continued to fall, reaching a level of 166/114, and the thiocyanate concentration had risen to 18.2 mg. per 100 c.c., so the dose of potassium thiocyanate was reduced to 0.2 Gm. twice daily. Shortly after this the patient was hospitalized for an acute exacerbation of her chronic cough, and did not take any thiocyanate for a period of three weeks. On her return to the clinic, the blood pressure was 194/114, and the dose of 0.2 Gm. twice daily was resumed. She has since been maintained on the thiocyanate treatment; the dosage has been determined by the blood level, except for an occasional period when she has not returned to the clinic for care. After these latter periods, a resumption of the high level of the blood pressure occurs, but not to as high a level as during the original observation

period. Her present dose varies from 0.1 Gm. twice daily to 0.2 Gm. twice daily, and the blood thiocyanate levels have been between 6.3 mg. and 11.4 mg. per 100 c.c. without any evidence of toxicity.

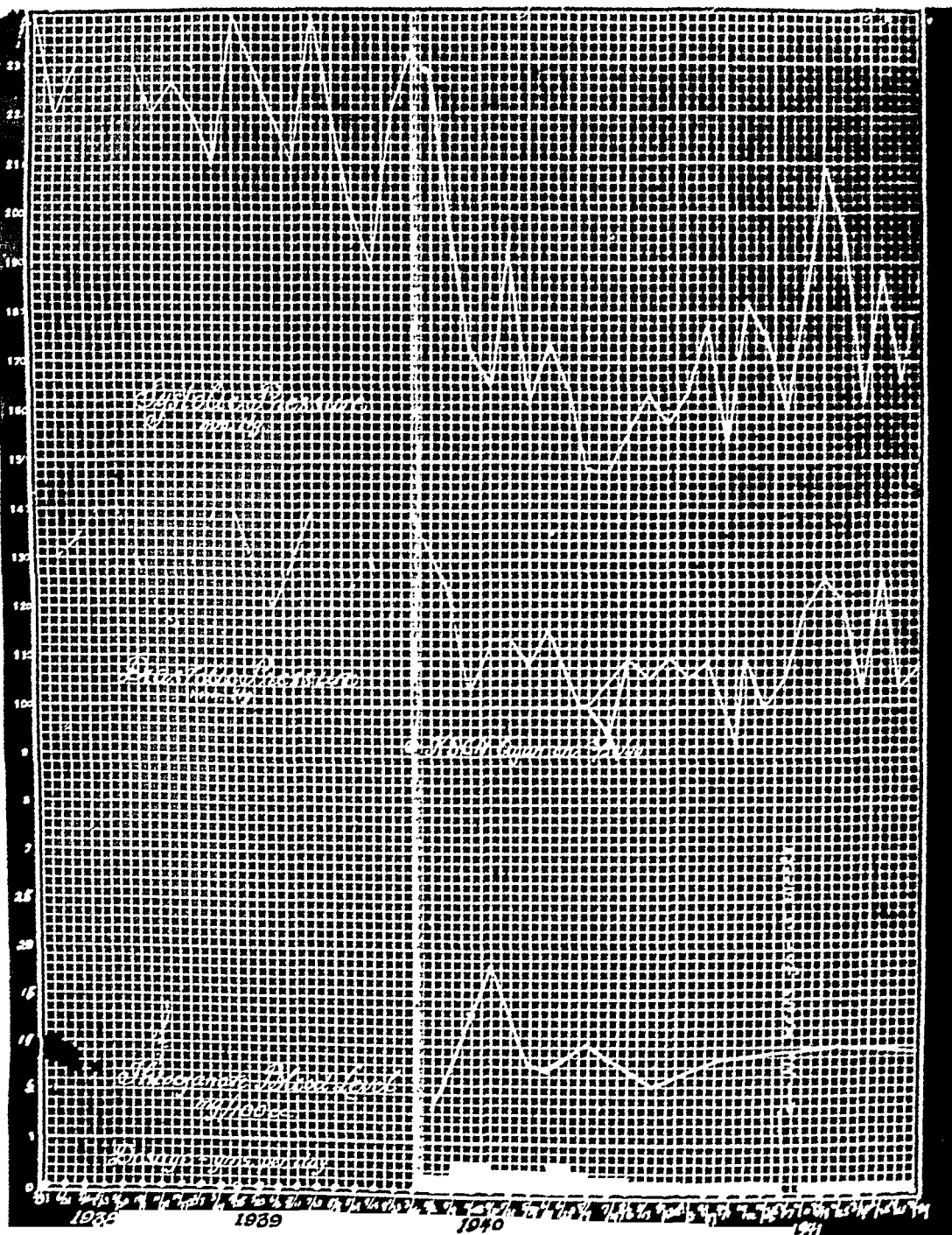Fig. 1 demonstrates the variations in blood pressure before and after therapy with thiocyanate.

Fig. 1.—Case 1. Systolic and diastolic blood pressure before and after instituting thiocyanate treatment. Daily dose of the drug and blood levels are also shown.

CASE 2.—(Fig. 2.) B. W., a woman, aged 52 years, was admitted to the clinic April 5, 1938, complaining of precordial pain, headaches, dizziness, and some tinnitus. She had just been discharged from the ward, where the diagnoses were: (a) hypertension and arteriosclerosis, (b) enlarged heart, myocardial fibrosis, and coronary sclerosis, (c) regular
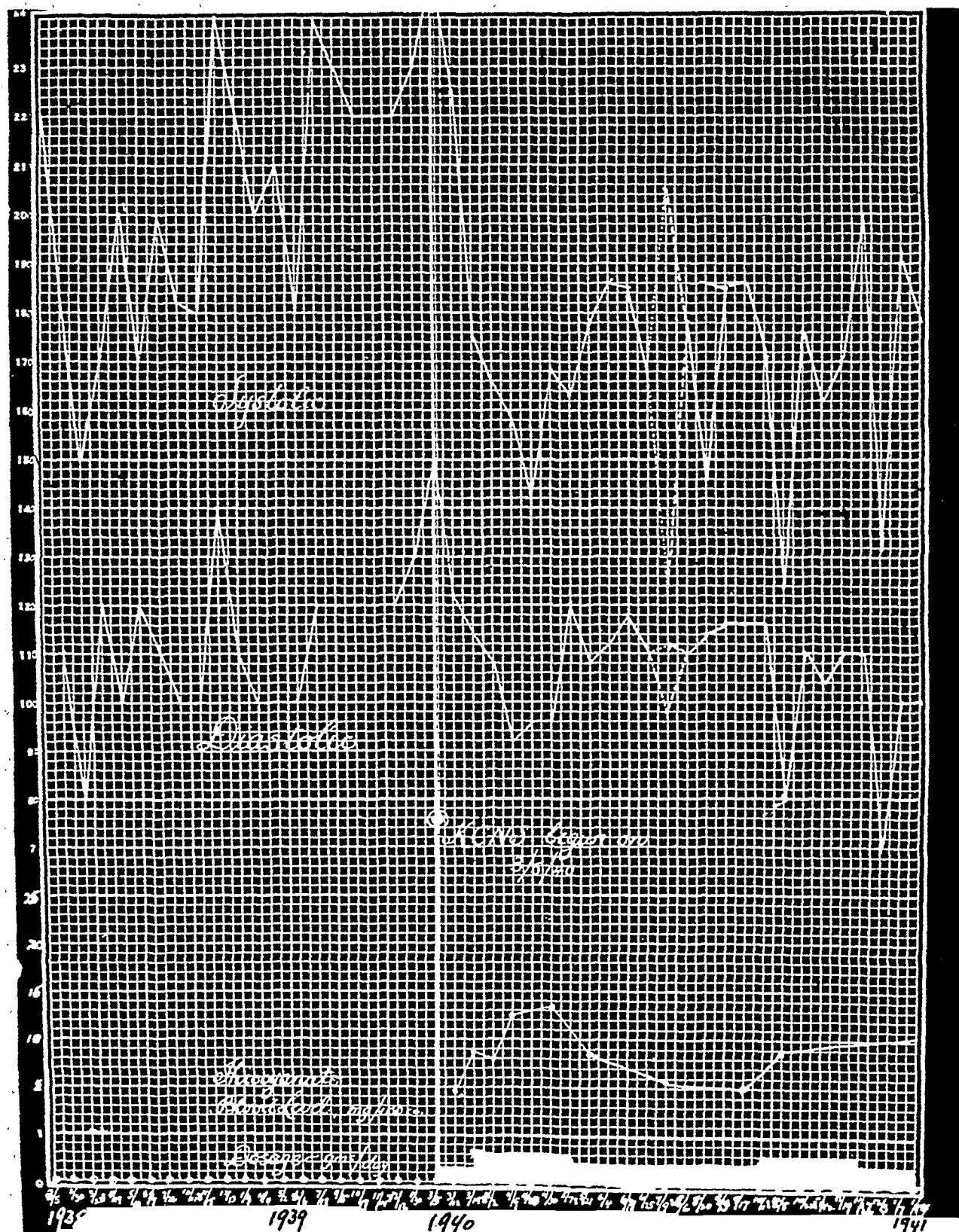
Fig. 2.—Course in Case 2.

sinus rhythm, (d) Class III C, and (e) obesity. The blood pressure on admission was 170/110. The urine concentrated to 1.022 and was entirely normal. The phenolsulfonphthalein excretion was 55 per cent in three hours. The nonprotein nitrogen of the blood was 32 mg. per 100 c.c., and the sugar, 118 mg. per 100 c.c.; the blood Wassermann reaction was negative. The hemoglobin was 75 per cent, the erythrocyte count, 3.3 million per cu. mm., and the leucocyte count, 8,000 per cu. mm., with 60 per cent polymorphonuclear cells. A teleroentgenogram revealed marked enlargement of both cardiac diameters, and the electrocardiogram showed evidence of myocardial damage and deviation of the electrical axis to the left.

She was placed on a 1,000-calorie diet, and was treated with phenobarbital and a mixture of sodium bromide and chloral hydrate. During this time her blood pressure showed marked evidence of fluctuation; the systolic pressure varied from 170 to 240, and the diastolic, from 100 to 140. In addition, the patient, during the period of observation, had numerous, sudden attacks of "fainting," associated with shortness of breath and followed by profuse perspiration and vomiting. There was also evidence of emotional imbalance during the attacks.

Some of these attacks which occurred while she was in the clinic were observed by us, and had no definite pattern. Neurological examination was reported as negative. There was no evidence of gall bladder disease, and the otolaryngologist reported nothing unusual about her vestibular apparatus. It was concluded that these attacks were related to the hypertension, probably a result of encephalopathy.

Potassium thiocyanate therapy was started after an observation period of two years. The initial dose was 0.1 Gm. three times a day. The blood pressure at the time was 250/150. One week later the blood contained 4.4 mg. of thiocyanate per 100 c.c. and the pressure had fallen to 226/122. The same dose of potassium thiocyanate was continued, and the next week the blood pressure was 176/114. The dose was increased to 0.2 Gm. three times daily, and, a week later, the blood pressure had fallen to 166/108 and the blood thiocyanate level was 8.7 mg. per 100 c.c. She has now been maintained on the thiocyanate treatment for almost two years; the thiocyanate level is maintained between 5 mg. and 13.3 mg. per 100 c.c.

This patient still shows marked lability of the blood pressure, with wide fluctuations; the general range, however, is considerably lower. In addition, there has been almost complete cessation of the "fainting" attacks described above; their occurrence has decreased to intervals of several months, whereas previously they had manifested themselves twice and three times weekly.

CASE 3.—(Fig. 3.) B. R., a man, aged 51 years, was first seen in the clinic on Dec. 28, 1937. He was admitted with complaints of generalized, throbbing headaches, poor memory, dizziness, dyspnea, orthopnea, palpitation, precordial pain, nocturia, and fatigue. The blood pressure on admission was 238/130. A teleroentgenogram revealed enlargement of the heart in all diameters, accentuation of the left ventricular curve, and dilatation and tortuosity of the aorta. The electrocardiogram showed deviation of the electrical axis to the left. A pyelogram made at another hospital had been reported as showing some shagginess of the calyces of the right pelvis. Excretion pyelograms made when the patient was admitted to the ward showed that both kidneys were normal in size, shape, and position. The pelves, calyces, and ureters were normal
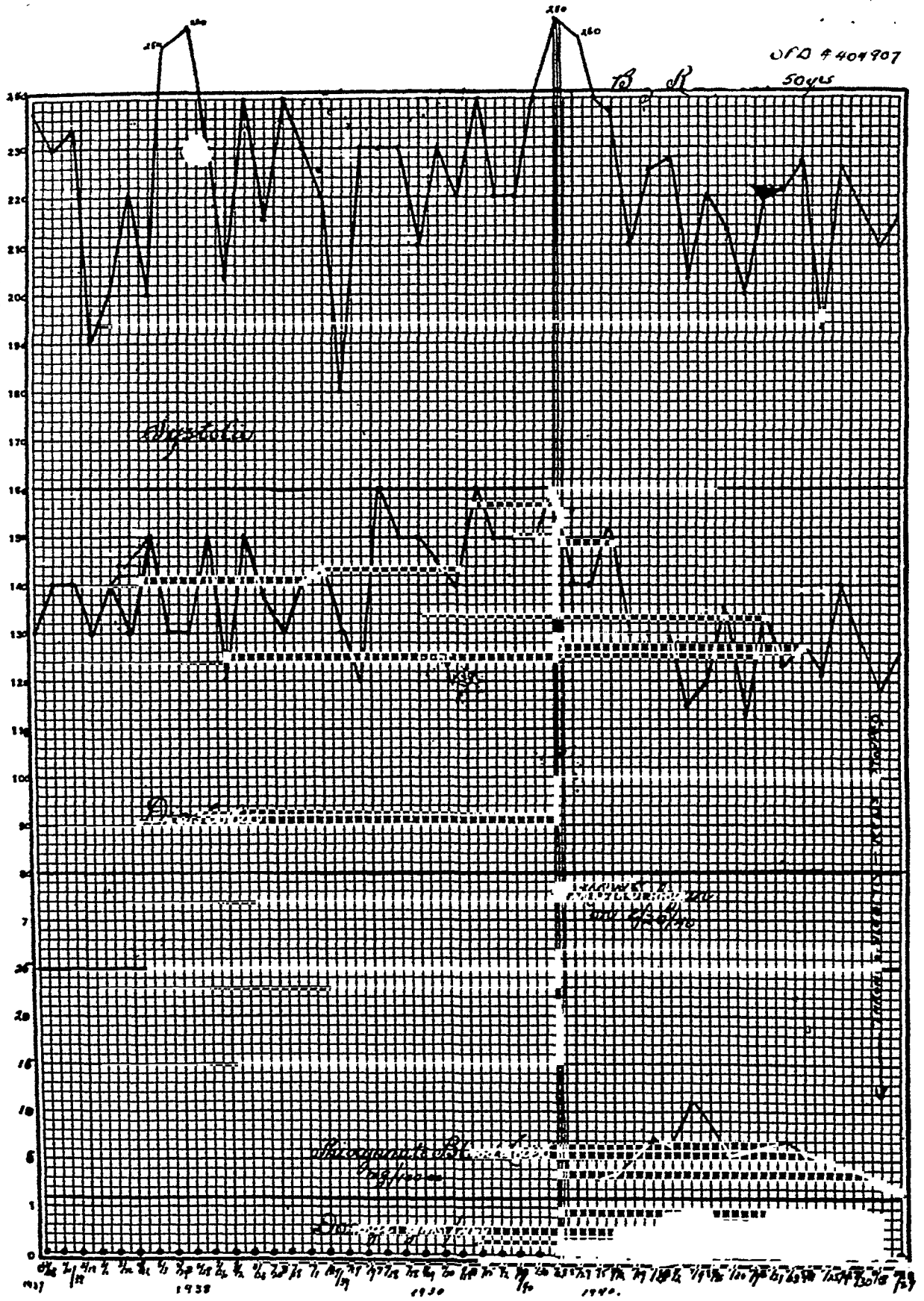
Fig. 3.—Course in Case 3.

on both sides. The electrocardiogram showed sinus rhythm and deviation of the electrical axis to the left. The blood Wassermann reaction was negative, the hemoglobin was 85 per cent, the erythrocyte count was 4.65 million, and the leucocyte count was 6,600 per cu. mm., with 80 per cent polymorphonuclears and 20 per cent lymphocytes. The nonprotein nitrogen of the blood was 31 mg. per 100 c.c., the creatinine, 2, and the uric acid, 3.6. The urine had a specific gravity of 1.018 and contained a trace of albumin. Occasional hyaline and granular casts were seen on microscopic examination, as well as an occasional erythrocyte and 2 to 3 leucocytes per high-power field.

After a period of observation of slightly over three years, during which time the systolic blood pressure was persistently at 190 to 260 and the diastolic at 130 to 150, he was started on potassium thiocyanate therapy. The initial dose was 0.1 Gm. three times a day, and, after a week, a blood level of 4 mg. of thiocyanate per 100 c.c. was reached. The blood pressure, however, remained at 257/140. On the same dose, a week later, the blood pressure was 232/140, and the blood thiocyanate, 4.2 mg. per 100 c.c. Slight dermatitis of the scalp was noted, but it was decided to continue the thiocyanate therapy, and the dose was increased to 0.2 Gm. three times daily. A week later, the thiocyanate level in the blood was 6.9 mg. per 100 c.c., but the blood pressure remained elevated (226/130). The dermatitis had disappeared, and the patient claimed that he was better because the severe headaches had abated, so the dose was increased again to 0.3 Gm. three times daily. There was no increase in the blood thiocyanate; the concentration remained at 6.45 mg. per 100 c.c. The blood pressure was still high, so that he was given 0.4 Gm. three times a day, a total of 1.2 Gm. daily. This time he reached a level of 10.8 mg. thiocyanate per 100 c.c. There was no perceptible lowering of the blood pressure. The dose of 1.2 Gm. daily was continued for two weeks, when he began to have some nausea and loss of appetite, and it was decreased to 0.3 Gm. three times a day, lowering the concentration of thiocyanate in the blood to 5.5 mg. per 100 c.c. The blood pressure had not been lowered at all, but, since the patient stated that he felt better while taking the medicine, it was continued.

CASE 4.—(Fig. 4.) M. D., a woman, aged 52 years, was admitted to the clinic Jan. 9, 1940, with headache, giddiness, dyspnea, palpitation, and precordial pain radiating to the left shoulder. The blood pressure was 212/108. Fluoroscopic examination revealed that the heart was normal in size and the chambers normal in contour. The electrocardiogram revealed no abnormalities. The blood nonprotein nitrogen was 36, the creatinine, 1.7, and the uric acid, 3.7 mg. per 100 c.c. The urine specific gravity was 1.015; the urine contained a very faint trace of albumin, and, on microscopic examination, a few clumps of leucocytes were seen. The diagnosis was essential hypertension with no evidence of cardiac involvement.

After a short period of observation, during which the blood pressure was between 204 and 212, systolic, and 108 and 118, diastolic, she was placed on thiocyanate treatment. The usual initial dose of 0.1 Gm. three times daily was given for one week, and she returned to the clinic complaining of nausea, vomiting, loss of appetite, dizziness, and weakness. The blood pressure had fallen to 154/92, and the thiocyanate was found to be 12.5 mg. per 100 c.c. blood. The potassium thiocyanate was discontinued and then started again in a dose of only 0.1 Gm. daily.

The blood pressure has remained low with a dose varying between 0.1 Gm. daily and 0.1 Gm. twice daily; the systolic ranged between 150 and 160, and the diastolic, between 90 and 100. The thiocyanate concentration in the blood with this dose has varied between 5.9 and 7.3 mg. per 100 c.c. Ten months after the thiocyanate had been started she developed a dermatitis, and the drug was stopped, whereupon the blood
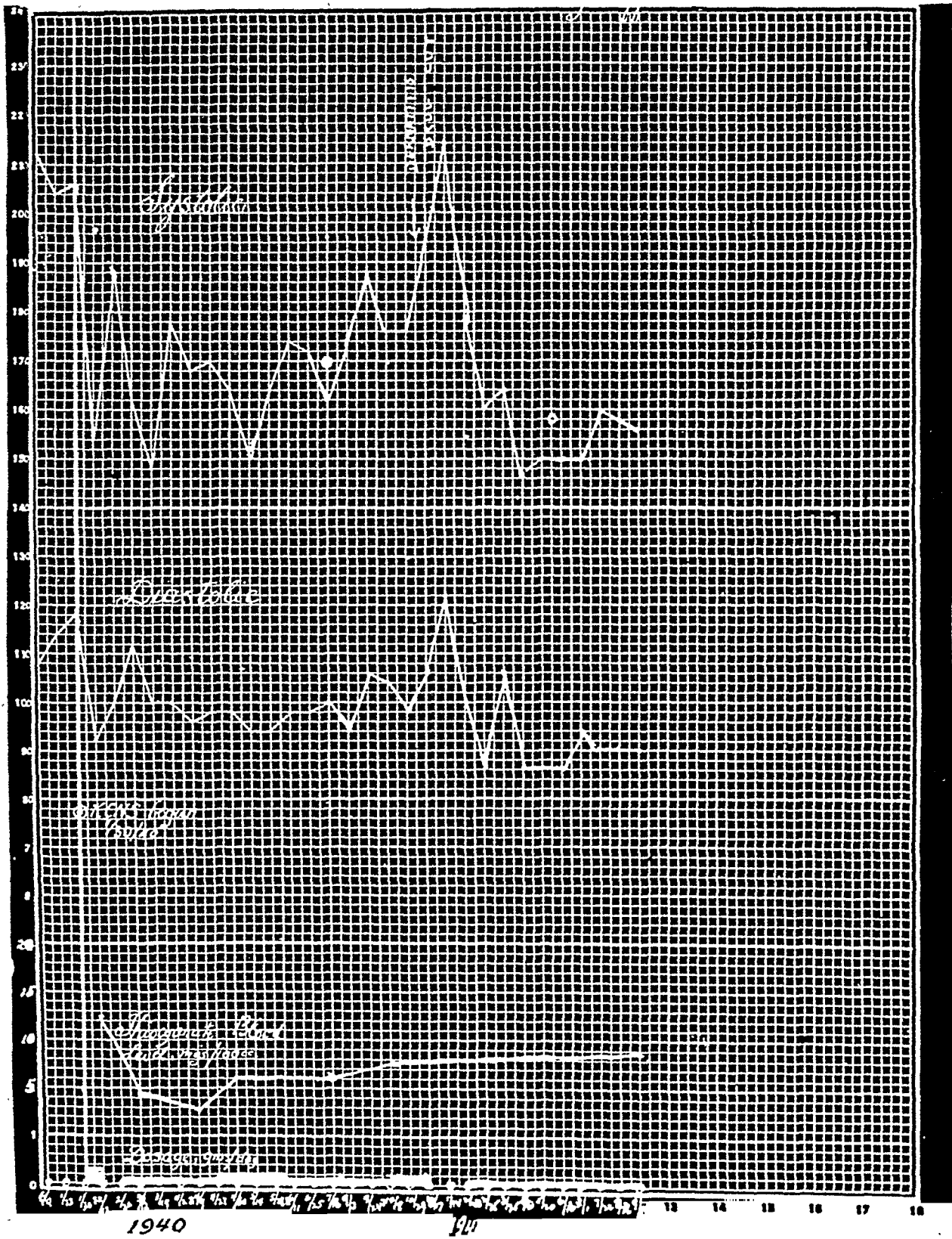

Fig. 4.—Course in Case 4.

pressure rose to 210/120. After the dermatitis cleared up, thiocyanate treatment was started again and the blood pressure fell to the previous low level.

CASE 5.—(Fig. 5.) E. P., a woman, aged 62 years, was admitted to the clinic Oct. 24, 1939, with a history of nocturnal attacks of paroxysmal

Fig. 5.—Course in Case 5.

dyspnea and substernal oppression of eight months' duration. The heart on roentgenologic examination was enlarged in all diameters; there was accentuation of the left ventricular curve, and the size and shape of the aorta were within normal limits. The blood Wassermann reaction was negative, the nonprotein nitrogen was 45 mg., the sugar, 100 mg., the uric acid, 4.4 mg., and the creatinine, 2.7 mg. per 100 c.c. The urine showed a specific gravity between 1.009 and 1.026, 1 plus albumin, and an occasional granular cast. The electrocardiogram showed regular sinus rhythm and deviation of the electrical axis to the left.

After a control period of seven months, during which the blood pressure ranged between 160 and 210, systolic, and 100 and 140, diastolic, she was started on potassium thiocyanate therapy. In spite of an adequate concentration of thiocyanate in the blood, there was no appreciable lowering of the blood pressure. This can best be appreciated by a study of the chart, in which it is to be noted that, although occasionally there was a lowering of the blood pressure during thiocyanate therapy, similar changes occurred with nonspecific treatment.

COMMENT

These cases have been selected to demonstrate the results obtained in the entire series. Approximately fifty per cent of the patients showed an appreciable lowering of the blood pressure. A few of the patients, as in Case 3, claimed to be subjectively improved while taking the thiocyanate in spite of maintenance of the high level of blood pressure. This is a factor that is very difficult to evaluate, and may be entirely suggestive.

Case 4 illustrates the fact that optimum blood levels can be maintained with comparatively small doses. Moreover, dangerously high blood concentrations may be reached with average doses. The importance of determining the thiocyanate concentration in the blood at fairly frequent intervals during therapy cannot be stressed too strongly.

The marked lability of the blood pressure in all of the cases can be seen from a study of the figures. Although, occasionally, lowering of the blood pressure is observed during treatment, similar instances are seen to have occurred without any specific therapy.

This illustrates the importance of an adequate period of observation of the patient on various methods of treatment before studying the value of any newer form of therapy.

No fatalities and no dangerous toxic effects were observed. This is accounted for by the fact that the patients were seen every week during the first few weeks of thiocyanate therapy, and frequent blood thiocyanate determinations were made. In this way, early toxic symptoms, as well as the appearance of an abnormally high blood level, could be detected and treated before dangerous symptoms supervened.

EXPERIMENTAL WORK

In the course of our studies, it occurred to us that, since the patients were taking the drug in divided doses, blood specimens taken in vary-

ing time relation to the ingestion of the drug might give us different results with respect to the thiocyanate content of the blood. It was decided to study this possibility in the following manner: After the patients had been stabilized with regard to the thiocyanate dosage and blood level, they were asked to come to the laboratory in the morning before taking any of the drug. On arrival at the clinic laboratory, a blood specimen was removed which we termed the "fasting specimen." The patient then took the prescribed dose and specimens were removed at one-, two-, and three-hour intervals. A second dose of the drug was again administered, and blood specimens removed one hour and three hours later. All six specimens were then analyzed for their thiocyanate content. As is evident from a study of the figures in Table I, there was no material change in the blood concentration throughout the twenty-four hours, irrespective of the amount of the drug that the patient was taking.

TABLE I

BLOOD THIOCYANATE LEVELS

CASE NUMBER	FASTING SPECIMEN	ONE HOUR AFTER FIRST DOSE	TWO HOURS AFTER FIRST DOSE	THREE HOURS AFTER FIRST DOSE	ONE HOUR AFTER SECOND DOSE	THREE HOURS AFTER SECOND DOSE
			Mg. per 100 c.c. Blood			
1	15.4	12.9	12.9	12.9	13.8	14.3
2	12.9	12.9	12.9	12.9	12.9	13.8
3	9.7	10.3	10.8	11.4	10.3	10.8
4	18.0	18.0	19.0	19.0	19.3	19.0

Whether or not the blood concentration of thiocyanate varies appreciably throughout the day was checked in still another fashion. This time hospitalized patients were utilized, and blood specimens were taken at 4-hour intervals during the day; that is, at 8:00 A.M., 12 M., 4:00 P.M., and 8:00 P.M., irrespective of the time at which the medicine was taken and regardless of the frequency of administration, whether twice or three times daily.

The results of this study are tabulated in Table II. Here again there was a fairly constant level of the thiocyanate concentration in the blood throughout the day.

TABLE II

BLOOD THIOCYANATE LEVELS AT INTERVALS DURING THE DAY, IRRESPECTIVE OF THE TIME AT WHICH THE MEDICINE WAS TAKEN

CASE NUMBER	8:00 A.M.	12 M.	4:00 P.M.	8:00 P.M.
		Mg. per 100 c.c. Blood		
1	6.9	7.3	4.8	7.3
2	12.1	11.8	12.5	–
3	7.7	9.3	8.2	–
4	8.4	8.7	8.9	8.9
5	5.9	6.3	6.5	6.3
6	4.7	5.3	5.0	5.6

The constancy of the blood level made it appear that absorption and excretion occurred at equal rates. We therefore decided to study this problem further by comparing the daily twenty-four-hour urinary output of the drug with the daily intake.

URINARY EXCRETION OF THIOCYANATE COMPARED WITH DAILY INTAKE

For the purpose of this study, six patients were hospitalized so that they could be observed closely and all of their urine collected. The dose of thiocyanate in Cases 1, 2, 3, and 4 had previously been ascertained, so that an optimum blood concentration had been reached. In Cases 5 and 6, as can be seen from the rising blood concentration, the patients had just started on the drug. In all patients, a daily blood concentration was determined, and the entire urinary output in each twenty-four hours was collected separately. By filtering the urine through animal charcoal, a clear solution was obtained, and the concentration of thiocyanate was easily determined. The daily output could then be calculated.

TABLE III

COMPOSITE STUDY* OF DAILY INTAKE OF THIOCYANATE, THE BLOOD CONCENTRATION, AND THE URINARY EXCRETION

	DAILY DOSE		BLOOD CONCEN- TRATION	URINE		
DATE	AS KCNS. (GM.)	AS CNS. (MG.)		VOLUME (C.C.)	MG. CNS. PER 100 C.C.	TWENTY- FOUR-HOUR OUTPUT (MG.)
8/ 7/41	0.4	239	7.4			
8/ 8/41	0.4	239	7.4	1,100	11.8	129.8
8/ 9/41	0.4	239	8.4	1,900	11.8	224.2
8/10/41	0.4	239		1,500	4.3	64.5
8/11/41	0.4	239		1,400	6.5	91.0
8/12/41	0.4	239	8.0	1,900	4.9	93.1
8/13/41	0.4	239	7.9	1,400	4.5	63.0
8/14/41	0.4	239	8.4	1,000	3.7	37.0

*The subject of this study was B. W., a woman, aged 51 years (Case 1).

In Case 1 (Table III), on a constant daily dose of 0.4 Gm. of potassium thiocyanate, or 239 mg. calculated as thiocyanate ion, a fairly constant blood concentration was maintained; the variation was from 7.4 to 8.4. However, marked variation was found in the urinary output, namely, from as low as 37 mg. to as high as 224.2 mg.

In Case 2 (Table IV), a fairly constant blood level was also maintained; the range was from 6.3 to 8.7 mg. per 100 c.c. Here, again, a marked variation in urinary output was found; the figures ranged from 54.6 mg. to 287.5 mg.

In Case 3 (Table V), such marked variation in excretion was not found, but the amount excreted was only a small part of the amount ingested.

In Case 4 (Table VI) there was also marked variation in the urinary thiocyanate output.

TABLE IV

COMPOSITE STUDY* OF DAILY INTAKE OF THIOCYANATE, THE BLOOD CONCENTRATION, AND THE URINARY EXCRETION

DATE	DAILY DOSE		BLOOD CONCEN-TRATION	URINE		
	AS KCNS. (GM.)	AS CNS. (MG.)		VOLUME (C.C.)	MG. CNS. PER 100 C.C.	TWENTY-FOUR-HOUR OUTPUT (MG.)
7/28/41	0.2	358	8.0			
7/29/41	0.6	358	8.1	515	15.4	79.3
7/30/41	0.6	358	8.7			
7/31/41	0.6	358	8.0	1,150	18.2	209.3
8/ 1/41	0.6	358	7.1	700	30.8	215.6
8/ 2/41	0.6	358	6.3	1,150	25.0	287.5
8/ 3/41	0.6	358		375	16.7	62.6
8/ 4/41	0.6	358	6.5	300	18.2	54.6
8/ 5/41	0.6	358	6.7	700	16.7	116.9
8/ 6/41	0.6	358	7.7	850	20.0	170.0

*The subject of this study was B. G., a woman, aged 65 years (Case 2).

TABLE V

COMPOSITE STUDY* OF DAILY INTAKE OF THIOCYANATE, THE BLOOD CONCENTRATION, AND THE URINARY EXCRETION

DATE	DAILY DOSE		BLOOD CONCEN-TRATION	URINE		
	AS KCNS. (GM.)	AS CNS. (MG.)		VOLUME (C.C.)	MG. CNS. PER 100 C.C.	TWENTY-FOUR-HOUR OUTPUT (MG.)
7/30/41	0.2	120	7.7			
7/31/41	0.2	120	6.9			
8/ 1/41	0.2	120	6.3	500	13.3	66.5
8/ 2/41	0.2	120	6.1	350	20.0	70.0
8/ 3/41	0.2	120		478	12.2	58.3
8/ 4/41	0.2	120	5.1	325	13.3	43.2
8/ 5/41	0.2	120	5.1	600	11.8	70.8
8/ 6/41	0.2	120	4.9	400	10.5	42.0
8/ 7/41	0.2	120	5.4	425	9.3	39.5
8/ 8/41	0.2	120	4.7	400	7.4	29.6

*The subject of this study was M. K., a woman, aged 47 years (Case 3).

TABLE VI

COMPOSITE STUDY* OF DAILY INTAKE OF THIOCYANATE, THE BLOOD CONCENTRATION, AND THE URINARY EXCRETION

DATE	DAILY DOSE		BLOOD CONCEN-TRATION	URINE		
	AS KCNS. (GM.)	AS CNS. (MG.)		VOLUME (C.C.)	MG. CNS. PER 100 C.C.	TWENTY-FOUR-HOUR OUTPUT (MG.)
7/31/41	0.3	179	6.9			
8/ 1/41	0.3	179	6.1	1,650	8.2	135.3
8/ 2/41	0.3	179	6.1	1,050	5.0	52.5
8/ 3/41	0.3	179		1,050	8.7	91.3
8/ 4/41	0.3	179	6.3	950	3.5	33.2
8/ 5/41	0.3	179	5.9	1,400	3.5	49.0
8/ 6/41	0.3	179	5.7	1,600	4.6	73.6
8/ 7/41	0.3	179	6.5	1,600	5.4	86.4
8/ 8/41	0.3	179	5.9	1,600	5.3	84.8

*The subject of this study was M. J., a woman, aged 63 years (Case 4).

TABLE VII

COMPOSITE STUDY* OF DAILY INTAKE OF THIOCYANATE, THE BLOOD CONCENTRATION,
AND THE URINARY EXCRETION

DATE	DAILY DOSE		BLOOD CONCEN- TRATION	URINE		
	AS KCNS. (GM.)	AS CNS. (MG.)		VOLUME (C.C.)	MG. CNS. PER 100 C.C.	TWENTY- FOUR-HOUR OUTPUT (MG.)
8/ 7/41	0.3	179	1.7	1,725	2.1	36.2
8/ 8/41	0.3	179	2.4	1,850	3.0	55.5
8/ 9/41	0.3	179	2.7	2,400	2.1	50.4
8/10/41	0.3	179		1,800	4.3	77.4
8/11/41	0.3	179				
8/12/41	0.3	179	4.3	950	9.1	86.4
8/13/41	0.3	179	4.5	2,000	3.7	74.0
8/14/41	0.3	179	5.0	2,000	3.6	72.0
8/15/41	0.3	179	4.7		5.3	
8/16/41	0.3	179	5.3	1,870	4.7	87.9
8/17/41	0.3	179		2,000	3.9	78.0
8/18/41	0.3	179	6.9	2,000	5.1	102.0

*The subject of this study was B. R., a man, aged 51 years (Case 5).

TABLE VIII

COMPOSITE STUDY* OF DAILY INTAKE OF THIOCYANATE, THE BLOOD CONCENTRATION,
AND THE URINARY EXCRETION

DATE	DAILY DOSE		BLOOD CONCEN- TRATION	URINE		
	AS KCNS. (GM.)	AS CNS. (MG.)		VOLUME (C.C.)	MG. CNS. PER 100 C.C.	TWENTY- FOUR-HOUR OUTPUT (MG.)
7/28/41	0.3	179	1.8			
7/29/41	0.3	179		550	3.3	18.1
7/30/41	0.3	179	3.6	480	25.0	120.0
7/31/41	0.3	179	3.3			
8/ 1/41	0.3	179	4.0	960	5.5	52.8
8/ 2/41	0.3	179	4.3	1,020	5.6	57.1
8/ 3/41	0.3	179		900	5.6	50.4
8/ 4/41	0.3	179	5.4	1,080	6.9	74.5
8/ 5/41	0.3	179	5.3	640	9.3	59.5
8/ 6/41	0.6	358	5.6	420	6.7	28.1
8/ 7/41	0.6	358	6.1	600	8.2	49.2
8/ 8/41	0.6	358	7.1	700	6.3	44.1
8/ 9/41	0.6	358	11.1	600	6.5	39.0
8/10/41	0.6	358		600	5.9	35.4
8/11/41	0.6	358	8.6	600	4.3	25.8
8/12/41	0.6	358	11.1	650	8.6	55.9
8/13/41	0.6	358	12.1	175	15.4	26.9

*The subject of this study was I. L., a man, aged 58 years (Case 6).

In Cases 5 and 6 (Tables VII and VIII), the patients had been started
on the drug. As can be seen, the blood concentration shows a steady
rise to the optimum level. In Case 6, an increase in the daily dose was
required. Here again no correlation between urinary excretion and the
dosage was found.

This marked variation in the urinary output is rather difficult to ex-
plain in view of a fairly constant maintenance of the blood level. We
must conclude that other excretory routes are probably utilized. Gold-
ring and Chasis,[30] in comparing the urinary output of thiocyanate with

the daily intake, without following the blood levels, also concluded: "there appears to be a distinct lack of relationship between the average amount excreted per day and the average administered per day."

DISCUSSION

The mechanism of the action of the thiocyanates in the reduction of blood pressure is not clearly understood. Healy[25] observed a marked lowering of blood pressure in his cases, and, in some experiments on rabbits, obtained a strongly positive reaction for thiocyanate in the adrenal cortex. This led him to conclude that the effect is similar to a hypoadrenia. Lindberg, Wald, and Barker[16] gave toxic doses of thiocyanate to dogs, and obtained blood levels of 20 to 60 mg. per 100 c.c. They found a marked lowering in blood cholesterol, a fall in blood proteins, a definite fall in hemoglobin, hematocrit reading, and erythrocyte count. an aplastic condition of the bone marrow, and fatty degeneration of the liver. Routine examination of the myocardium, kidneys, spleen, pancreas, lungs, and thyroid showed no gross or microscopic alterations. Anatomic changes in the adrenals were lacking. Analysis showed no greater amount of thiocyanate in this organ than in the others. Blood studies in reference to sugar metabolism, sodium, potassium, and chlorides failed to disclose any evidence of change in adrenal function. They concluded: "We are unable to support the impression of Healy that hypoadrenia may be the principal feature of the toxicology of the thiocyanates."

The recent work of Caviness and his associates[24] is of interest. They report that thiocyanates are naturally present in the body in a much higher concentration than any other known depressor substances. They found a natural concentration of thiocyanate in 241 persons to whom the drug had never been administered of 0.31 to 2.55 mg. per 100 c.c. of blood, and that the blood pressure varied in inverse ratio to the blood thiocyanate concentration. They suggest that the thiocyanates help to counterbalance the effects of the pressor substances in the body, and conclude that the use of thiocyanates in hypertension need no longer be regarded as empirical.

Despite the accumulation of reports of thousands of patients treated with thiocyanate without fatality, death occasionally occurs, as in the case reported recently by Russell and Stahl.[27] Extreme caution should be used in selecting patients for treatment. Their patients would seem to have been a poor choice because of the greatly diminished kidney function, as evidenced by a urea clearance of 27 per cent of normal, a nonprotein nitrogen of 43 mg. per 100 c.c. of blood, and 3 plus albuminuria. Furthermore, poor judgment was shown in continuing the administration of thiocyanate to their patient when a level of 15.2 mg. had been reached. This is particularly important in view of the fact that the dose had not been changed, and that one week previously his blood level had been 4.5 mg. Such a rapid rise in blood concentration

is certain evidence of faulty excretion and cumulative action, and indicates immediate cessation of the drug. One can only conclude, as do Mandelbaum[28] and Ayman,[29] that this was an unfortunate choice of a patient, rather than a condemnation of the drug.

SUMMARY AND CONCLUSIONS

1. Thirty-nine ambulatory patients with hypertension were treated with thiocyanate. Approximately fifty per cent showed an appreciable lowering of the blood pressure, and a few others reported subjective improvement without any lowering of the blood pressure.

2. Ambulatory and hospital patients who were receiving potassium thiocyanate for hypertension were studied to ascertain whether the blood concentration of the drug varied during the day, or was affected by the relation of the time of ingestion to the time of taking the blood.

3. The blood level of thiocyanate remains fairly constant throughout the day.

4. Further studies were made to ascertain whether any relation existed between the daily intake or the blood concentration, on one hand, and the urinary output, on the other.

5. There is no correlation between the urinary output of thiocyanate and the daily intake or the blood concentration.

6. The exact mode of action of thiocyanate in hypertension is not clearly defined, and should be the subject of further investigation.

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POSTERIOR BASAL CARDIAC INFARCTION AFFECTING A YOUNG MAN, FOLLOWED A YEAR LATER BY ANTERIOR APICAL INFARCTION

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THE incidence of coronary thrombosis among young adults has become of increasing importance in recent years. Accordingly, we are reporting a case in which two attacks of coronary thrombosis took place just a year apart, the initial one when the patient was 39 years of age, and the second when he was 40 years. In addition, we have sought to collect the total number of cases of coronary occlusion among persons less than the age of 41 years which have been reported to date. Furthermore, we are publishing the electrocardiograms in our case because seldom is so distinct a demonstration available of the role which electrocardiography plays in determining the presence of myocardial infarction, its location, and the existence of the myocardial damage which remains after the acute process has progressed to healing.

In 1939, Master, Dack, and Jaffe,[1] reviewed 500 cases of myocardial infarction due to coronary thrombosis, including thirty-nine cases (7.8 per cent) in which the patients were less than the age of 40 years. Also, they cited literature including 221 instances of this condition among relatively young patients. Of these 221 patients, 106 were less than 40 years of age and 115 were less than 41 years. Inasmuch as none of their references bore a date later than 1938, our survey of the literature concerning coronary occlusion among persons less than 41 years of age has covered the years 1939 to 1943, inclusive. The series of Buchanan, Indelicato, and Primavera,[2] reported in 1939, included seven patients less than the age of 41 years. In the same year, Goodson and Willius[3] cited thirty cases of coronary thrombosis among patients less than the age of 40 years. In a study published in 1942, based on 100 patients, Smith, Sauls, and Ballew[4] found five who were less than 40 years of age. Bancker,[5] also in 1942, reported a series including five patients less than 40 (or 41, possibly) years old. Six isolated reports of cases[6-11] have appeared since 1939; all six of the patients were in the third decade of life. In reviewing cases encountered at the Mayo Clinic since 1939, we found that five cases of undoubted coronary occlusion, including the case we are reporting, occurred among patients less than 40 years of age; two of these patients were 38 and three were 39 years of age. Moreover, two reports of cases[12, 13] in foreign journals were listed in the *Quarterly Cumulative Index Medicus*, but copies of

the journals were not available to us. Exclusive of the latter, as far as our search disclosed, 318 cases of coronary occlusion among persons less than the age of 41 years have been reported to date. (Since this paper was written, French and Dock[14] have reported data on eighty cases of fatal coronary arteriosclerosis in young persons between the ages of 20 and 36 years.)

<div align="center">REPORT OF CASE</div>

On March 9, 1942, a man, aged 39 years, who gave no history of angina pectoris or hypertension, was admitted to the hospital complaining of severe, constricting substernal pain which had been present intermittently all of the previous night to such degree that he had been unable to sleep.

On examination, the patient was in obvious distress and had moderate pallor, but he exhibited no signs of shock. Results of examination of the lungs were negative. Examination of the heart revealed sounds of somewhat diminished intensity, normal rhythm, and a rate of 90 beats per minute. The blood pressure was 124/90. There were no other physical signs of significance. The leukocytes numbered 14,500 per cubic millimeter of blood. The erythrocyte sedimentation rate was 30 mm. at the end of one hour (Westergren). An electrocardiogram on the day of admission (Fig. 1, a) was characteristic of infarction of the posterior basal portion of the left ventricle.

During the next five days the patient's temperature was elevated, and sometimes reached 101° F. The erythrocyte sedimentation rate rose to 47 mm. in one hour on the third day, and 110 mm. in one hour on the fourth day. The electrocardiograms continued to show a classical Q_3T_3 pattern. By March 11, partial (2:1) heart block had developed, with a P-R interval of 0.26 second (Fig. 1, b, Lead III). This was still present the following day, although the P-R interval had shortened to 0.24 second. The block had disappeared by March 14. It was believed that the patient had suffered a massive myocardial infarction and that the prognosis was grave. However, after the first week, his recovery was rapid. The erythrocyte sedimentation rate had dropped to 55 mm. in one hour by March 24. The abnormality of the S-T segment progressively subsided (Fig. 1, c). The electrocardiogram on March 27 (Fig. 1, d) showed a typical late Q_3T_3 pattern. The patient was dismissed from the hospital on March 30.

The man was seen at intervals during the ensuing year, and his progress seemed satisfactory. In electrocardiograms taken on May 15, and July 16, 1942, and on Feb. 24, 1943 (Fig. 1, e), there was no deviation from the late Q_3T_3 pattern.

On March 13, 1943, the patient, now aged 40 years, was awakened from sleep at 5:00 A.M. by pain, without extension, in the left shoulder. Shortly, however, he began to have a bandlike constricting pain in the substernal region and the epigastrium; the pain became progressively severe. He was seen at 8:00 A.M. and was given ¼ grain (0.016 Gm.) of morphine, followed by 1/100 grain (0.00065 Gm.) of glyceryl trinitrate, neither of which relieved the pain. On admission to the hospital, the heart tones were of good quality, the cardiac rate was 90 beats per minute, and the rhythm was regular. The blood pressure was 120/84. The lungs were negative. The leukocytes numbered 19,000 per cubic millimeter of blood, and the erythrocyte sedimentation rate was 19 mm. in one hour. The electrocardiogram (Fig. 1, f), compared to the last

previous tracing (Fig. 1, e), revealed marked decrease in the amplitude of the T waves in Leads I, IVR, and CR_2, and diminution in the depth of the inverted T waves in Leads II and III.

The patient was still in considerable distress at noon, seven hours after the onset, and repeated doses of morphine were required to control the pain. Vomiting occurred several times in the first few hours. With morphine and oxygen, the man was kept reasonably comfortable and the pain had subsided by midafternoon. It was believed that he had suffered a secondary coronary occlusion, and that this time the infarction was involving the anterior apical portion of the left ventricle, as indicated by the electrocardiographic changes.

On March 14, 1943, the heart tones were of poor quality, there was gallop rhythm, a loud pericardial friction rub was audible, and the apex had moved out beyond the nipple line. These signs suggested marked dilatation of the left ventricle. The blood pressure was 110/80. There were moist râles at the bases of the lungs. Treatment with digitalis
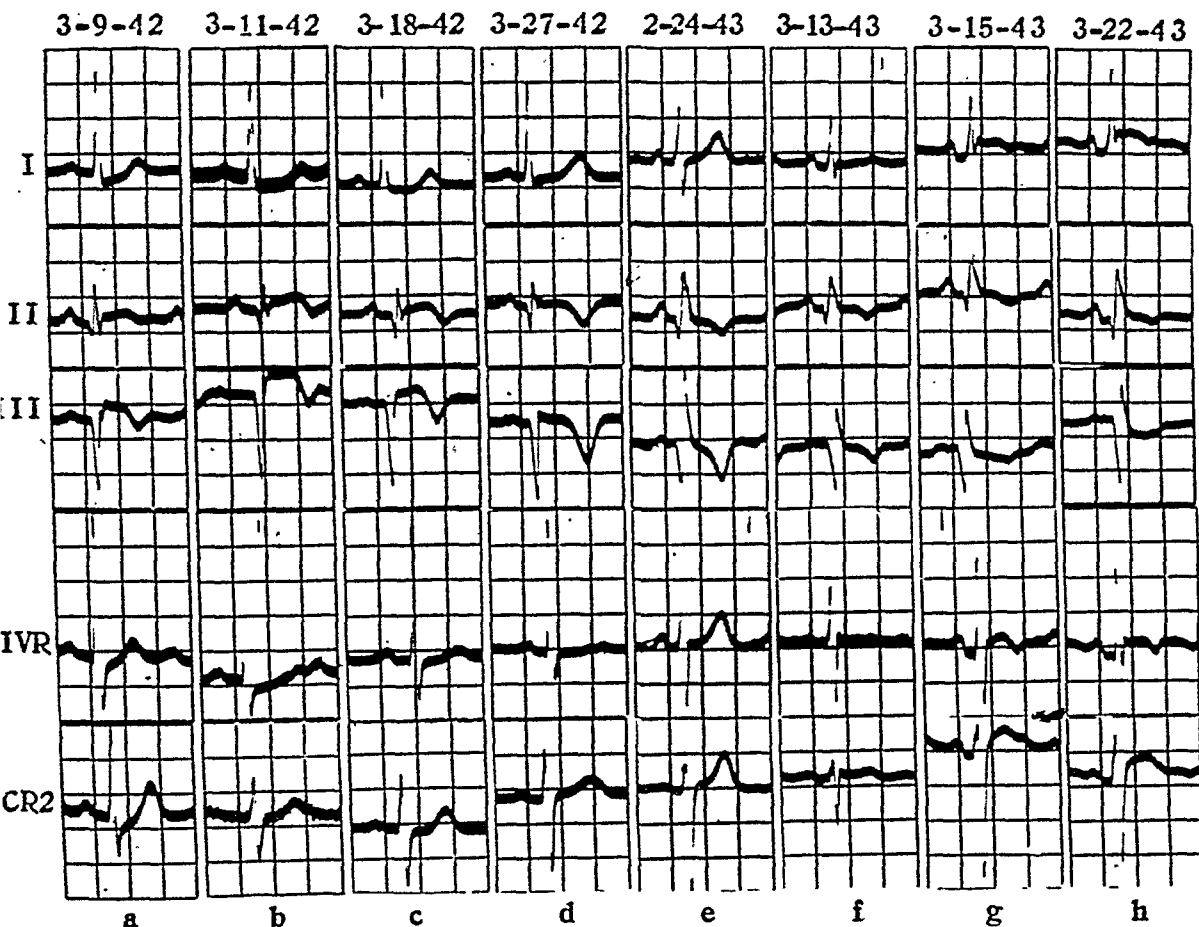
Fig. 1.—Electrocardiographic patterns indicative of posterior basal infarction of the left ventricle, followed a year later by anterior apical infarction:

a, Lengthened Q_3; elevated S-T_2 and S-T_3, depressed S-T_1; inverted T_3 and diphasic T_2; depressed S-T segment in Leads IVR and CR_2.

b, Delayed A-V conduction (P-R, 0.26 second in Lead III); T_2 now frankly inverted.

c, S-T segments returning toward isoelectric line.

d, Further progress of S-T segments toward isoelectric level. Note increased amplitude of inverted T_2 and T_3, and reciprocal, increased positivity of T_1.

e, Seventeen days before second occlusion. Typical late Q_3T_3 pattern

f, Tracing on day of second occlusion. Marked decrease in amplitude of T in Leads I, IVR, and CR_2; also, decreased negativity of T_2 and T_3.

g, Elevated S-T segments in Leads I and CR_2, depressed S-T_3; T inverted in Leads I and IVR; decreasing negativity of T_2 and T_3.

h, S-T segment deviations more marked in all leads. Pattern is now quite typically that of acute anterior apical infarction superimposed on the previous posterior basal infarction.

was instituted. On the next day, the erythrocyte sedimentation rate had risen to 80 mm. in one hour.

On March 22, severe anterior thoracic pain recurred and extended into both arms. This symptom was accompanied by pallor and sweating, and the pulse became feeble and rapid. The blood pressure was 86/72. It was believed that the infarct had extended and that a fatal issue was inevitable. However, on the following day the patient appeared definitely better; the heart tones were of better quality and the rate was slower. This improvement continued, although the erythrocyte sedimentation rate rose to 106 mm. in one hour on March 26.

After the attack of March 13, 1943, the electrocardiograms had continued to show a progression of changes indicating that the pattern of infarction of the anterior apical portion of the left ventricle was being superimposed on that of the previous posterior basal infarction. In the tracing on March 15 (Fig. 1, g), there had been an elevated S-T segment and an inverted T wave in Lead I, depression of the S-T segment in Lead III, and flattening of the previously inverted T waves in Leads II and III, and the outstanding changes in the chest leads consisted of an inverted T wave in IVR and elevation of the S-T segment in CR_2. All of these changes had been more marked in the tracing taken on March 22 (Fig. 1, h).

On April 11, the patient complained of vague pains in the anterior part of the thorax which were worse with inspiration and limited the respiratory excursions. He had a chill and his temperature rose to 101° F. That evening there were physical signs of consolidation over the lower part of the left lung, posteriorly. The leukocyte count was 20,600 per cubic millimeter of blood. A roentgenogram of the thorax revealed opacity over the lower half of the left pulmonary field, with evidence of some fluid. These abnormalities were interpreted as being due, in all probability, to consolidation subsequent to pulmonary embolism and infarction. The patient tolerated this complication unusually well; there was no febrile reaction after the first day, and specific treatment was not necessary. The physical signs gradually resolved.

The remainder of the patient's stay in the hospital was uneventful, as gradual improvement took place. On April 19, the erythrocyte sedimentation rate had dropped to 44 mm. in one hour. The heart remained enlarged, with the apex beat visible in the anterior axillary line. A loud, blowing, systolic murmur developed and persisted at the apex. Electrocardiograms taken later than those shown in Fig. 1 revealed a combination of the late Q_2T_2 and late T_1 patterns; the S-T segments in all leads had returned to the isoelectric level. The patient was dismissed from the hospital on May 7. At the time this report was written he was able to be up and about a small part of the time, but he had practically no cardiac reserve and he was close to congestive failure.

COMMENT

Hypertension and angina pectoris may be of less frequent occurrence in the histories of relatively young patients with coronary thrombosis than in the histories of older patients with this condition. Clawson[15] found that, among forty-eight patients less than 40 years of age who had coronary sclerosis severe enough to cause death, 19 per cent had accompanying hypertension, whereas, among those 40 years of age or

more, 46 per cent had hypertension. In White's[16] series there was no hypertension among patients (all males) less than 40 years of age, contrasting with a 25 per cent incidence of hypertension among patients of all ages. White found angina pectoris preceding coronary thrombosis among only 14 per cent of patients less than the age of 40 years, whereas, of 125 patients of all ages who had angina pectoris associated with coronary thrombosis, 76 per cent had angina before the thrombosis.

Smith, Sauls, and Ballew observed cardiac enlargement in 59 per cent of their cases of coronary thrombosis. Master, Dack, and Jaffe found this in 59.8 per cent of patients of all ages, but noted further that the incidence of cardiac enlargement was only 35.9 per cent among patients less than 40 years of age, and that, regardless of age, its incidence closely paralleled that of heart failure, which is the principal cause of death (considering all age groups) after coronary occlusion.

Smith, Sauls, and Ballew noted embolic phenomena in 10 per cent of their cases. Here again, Master, Dack, and Jaffe made a critical analysis which is illuminating. They observed that, among patients less than 50 years of age who suffer coronary thrombosis, the most frequent cause of death was arterial embolism, either peripheral or pulmonary; the death of 53 per cent of the patients in this age group was due to this cause, whereas the mortality due to this complication among those aged 50 years or more was only 12 per cent, and the cause of death was much more likely to be heart failure.

SUMMARY

According to our search of the literature, 318 cases of coronary thrombosis among patients less than 41 years of age have been reported. If we were able to validate two additional cases reported in foreign journals, the total would be brought to 320.

Our patient, whose case is here reported, suffered two attacks of coronary thrombosis. The first attack occurred at the age of 39 years, and resulted in infarction of the posterior basal portion of the left ventricle; the second occurred at the age of 40 years, and caused infarction of the anterior apical portion. The electrocardiograms depict the accuracy with which this diagnostic aid may reflect the presence and the location of myocardial infarction.

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ASSOCIATION OF HYPERTENSION AND MITRAL STENOSIS

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CERTAIN special relationships have been suggested regarding the development of hypertension in persons who have mitral stenosis. The first of these is that elevated blood pressure tends to ameliorate the clinical course of the valvular disability. Levine,[1] in considering this association, summarizes his views as follows: "Although it may add certain symptoms as a result of the hypertension itself, when these are not severe, there is reason to believe that it delays the progress of mitral stenosis. It is curious that so many patients with mitral stenosis over fifty years of age have hypertension in addition. I believe that hypertension prolongs their lives and enables them to reach the latter decades."

Levine suggests two factors as being possibly responsible for the beneficial effect which he notes. One is that the hypertension tends to induce and maintain enlargement and dilatation of the left ventricle, and that this dilatation opposes and delays the contraction of the mitral ring. The second factor which he considers is that the superimposition of hypertension upon mitral stenosis equalizes the burdens upon the two sides of the heart, and thus delays the development of an imbalance between them.

In addition to this salutory influence, it has been suggested that persons with mitral stenosis develop hypertension with greater frequency than do those of the general population. Levine feels that such an increased incidence occurs in the age range beyond 45 years, but that there is a tendency toward decreased blood pressure in the younger group of persons with mitral disease. He considers that a possible explanation is that the chronic rheumatic infection responsible for the valvular lesion may also insidiously produce widespread vascular damage which later results in hypertension. However, he thinks it more likely that certain persons have what he calls "vascular vulnerability," which renders them more susceptible to both rheumatic fever and the later development of hypertension.

Although the first of these two relationships is of greater clinical interest and largely conditions the interest in the latter, it will receive only subsidiary consideration here because of the limitations of the material available. The primary problem with which the present study is concerned is the relative frequency of the development of hypertension in persons with mitral stenosis.

The literature regarding the question is not voluminous. Boas and Fineberg,[2] in reviewing it in 1926, found that Bamberger, in 1857, had noted a frequent association of valvular heart disease and granular kidneys. Goodhart, in 1880, described the frequent occurence of granular kidneys in patients with mitral thickening and stenosis. Pitt, in 1888, surveying a large necropsy material, reported that one-third of females and one-fifth of males with mitral stenosis also had granular kidneys. Both Gibson and Coombs had noted the common occurrence of high arterial pressure in patients with mitral stenosis.

In conjunction with this review of the literature, Boas and Fineberg[2] reported a study of the blood pressure in 135 cases of mitral stenosis. Using a blood pressure in excess of 150, systolic, and 90, diastolic, as a criterion of hypertension, they found an incidence of 29 per cent (thirty-nine cases) in their total group whose age range was from 1 year to over 60 years of age. Sixty-seven of these were over 40 years of age, and, in this age range, the incidence of hypertension was 55 per cent. They compared these frequencies with the 11 per cent incidence in a group of 3,778 hospital patients who were unselected for age and sex.

Levine and Fulton[3] studied a series of 762 cases of mitral stenosis in which the ages ranged from 5 to over 70 years. One hundred fifty-nine of these patients were over 45 years, and, of them, ninety-two, or 58 per cent, had hypertension by the same criterion as that employed by Boas and Fineberg. Their conclusion was that "with advancing years patients with mitral stenosis have vascular hypertension with much greater frequency than the average population."

Brumm and Smith,[4] however, in reviewing 1,925 patients of all ages at the Mayo Clinic, found that only forty-four, or 2.3 per cent, had hypertension associated with mitral stenosis. Although their criterion of hypertension was not mentioned, it seems reasonable to assume from the fact that the lowest blood pressure in their hypertensive group was 152, systolic, and 90, diastolic, that it was approximately the same as that employed in the other two studies. They further concluded that the hypertension in these patients exerted no beneficial effect.

The material for the present study consists of cases of proved mitral stenosis, taken from the autopsy records of the pathology department of the University of Minnesota Medical School. Because of the possible mechanical effects of aortic valvular lesions upon blood pressure, all cases in which there was accompanying aortic valve involvement were excluded. However, in some instances there was an associated mitral regurgitation. All were cases of persons who died in Twin City hospitals during the period between 1929 and 1940. The blood pressures were taken from the hospital charts, either directly or as recorded on the autopsy reports; in those instances in which more than one blood pressure reading was recorded, the highest value was taken. Cases in which the patient was in coma or in which the blood pressure was taken within

twelve hours of death were excluded. The final group consisted of 144 cases with an age range of 20 to 87 years; forty-three (30 per cent) were males, and 101 (70 per cent) were females.

As a control group, a stratified sample of 288 cases, exactly matching the mitral group with respect to age and sex, was taken at random from the records of the out-patient clinic of the University Hospital. The blood pressures of these patients were those recorded at their initial physical examinations in the clinic.

Following the precedent of the studies noted above, a blood pressure in excess of 150, systolic, and 90, diastolic, was taken as the arbitrary criterion of hypertension. Because of the emphasis upon the factor of age by Levine and Fulton, their procedure of dividing the total group into two subgroups, with the age of 45 years as the point of division, was also employed here.

These conditions afford two bases of comparison between the mitral and control groups and between their respective subgroupings. They are first compared with regard to the frequency of the arbitrarily defined hypertension, and, second, on the basis of the average values for systolic and diastolic pressures.

The results of the first comparison for the total groups, for the subgroup over the age of 45, and for the subgroup under the age of 45 years are summarized in Table I. The differences observed are, in all cases, slight; the greatest critical ratio was 1.35, and therefore they fail to satisfy any of the criteria of statistical significance. In particular, the frequencies in which we are the most interested, namely, those for the age range over 45 years, are nearly identical for the mitral and control groups. As noted, the values are 30 and 31 per cent, respectively.

TABLE I

INCIDENCE OF HYPERTENSION IN MITRAL AND CONTROL GROUPS

	TOTAL		OVER AGE 45		UNDER AGE 45	
	MITRAL	CONTROL	MITRAL	CONTROL	MITRAL	CONTROL
Number of Cases	144	288	91	182	53	106
Number with Hypertension	34	62	27	56	7	6
Percentage with Hypertension	23.6	21.6	30	31	13	6
Standard deviation	3.6	2.4	4.9	3.4	4.6	2.3
	Difference 2		Difference 1		Difference 7	
	S. D.		S. D.		S. D.	
	difference 4.33		difference 5.96		difference 5.13	
	Critical		Critical		Critical	
	ratio .46		ratio .17		ratio 1.35	

This observed difference of 1 per cent is actually in the reverse direction from that expected and has a standard deviation of 5.96, which means that the chances that such a difference would occur by the accident of random sampling are about eighty-five in a hundred.

AVERAGE SYSTOLIC BLOOD PRESSURES FOR CONTROL AND MITRAL GROUPS

	TOTAL	OVER AGE 45	UNDER AGE 45
Control	139.86 ± 1.68	148.2 ± 2.34	125.5 ± 1.79
Mitral	138.9 ± 2.23	144.4 ± 3.02	129.6 ± 2.88
Difference	.96	3.8	4.1
S. D. difference	2.78	3.81	3.39
Critical, ratio	.34	1	1.2

TABLE III

AVERAGE DIASTOLIC PRESSURES FOR CONTROL AND MITRAL GROUPS

	TOTAL GROUP	OVER AGE 45	UNDER AGE 45
Control	85.7 ± .91	88.9 ± 1.09	80.3 ± 2.3
Mitral	84.4 ± 1.35	86.2 ± 1.75	81.5 ± 2.03
Difference	1.3	2.7	1.2
S. D. difference	1.68	2.05	2.3
Critical, ratio	.75	1.32	.52

A comparison of the mitral groups with their corresponding controls on a basis of average systolic and diastolic pressures (Tables II and III) likewise results in small differences which are not statistically significant. The highest critical ratio among these is 1.32. Here, too, the observed, slight difference for the subgroup over the age of 45 years is actually the opposite of that suggested. For the mitral group, the average blood pressure was 144.4 ± 3.02, systolic, and 86.2 ± 1.75, diastolic, as compared to the control values of 148.2 ± 2.34 and 88.9 ± 1.09.

An additional check upon the control group, averages of systolic and diastolic pressures, weighted for age and sex to correspond with the control group employed, were calculated from the values given by Wetherby.[5] These values were ascertained from a study of 5,540 persons of the same population from which the control group for the present study was selected. The averages thus calculated are 143, systolic, and 86, diastolic, and compare closely with the 139.86, systolic, and 85.7, diastolic, found in the present study. It does not appear therefore, that any considerable selective factor was operative in determining the present control group.

Finally, the mitral group of 144 cases was divided into those with hypertension and those without, and the average age at death of these two groups was compared. The average age at death for those with hypertension was 56.5 ± 2.19, and for those without, 48.9 ± 2.58. The difference of 7.6 ± 2.55 may be considered as bordering on statistical significance. However, it is not safe to conclude from this that the presence of hypertension confers an increased life expectancy upon a person with mitral disease. Hypertension and age are not independent variables; the former occurs with increasing frequency at higher ages, and, for that reason, the selection of a group on a basis of hypertension entails the artificial selection of those in the higher age range.

The objection may be raised that the blood pressures recorded for the autopsy group of cases of mitral stenosis are spuriously low because

they were taken after the onset of heart failure in most cases, and on hospitalized patients, whereas those for the control group were taken largely on ambulatory patients. An attempt was made to avoid the terminal fall in blood pressure by excluding those cases in which the recording was made within twelve hours of death. Furthermore, a fall in blood pressure with the onset of heart failure with mitral stenosis does not appear to be the rule. In considering this question, Fishberg[6] says, "Sometimes the systolic and pulse pressure fall slightly. More often the onset of heart failure in mitral stenosis is accompanied by a rise in the diastolic pressure with a smaller increase in systolic pressure." He also reports, "Lang and Manswetowa found that as a rule a break in compensation in cardiac disease is accompanied by a rise in arterial pressure which falls again as the heart improves. This was especially often the case in mitral disease and emphysema heart."

Finally, it seems unlikely that false readings due to the patients' condition would, in a group of this size, so exactly counterbalance an actual difference as to yield the observed close agreement.

CONCLUSIONS

It is somewhat hazardous to draw sweeping conclusions from small samples, however rigorous statistical precautions may be exercised. It appears, however, that the close agreements which were found in the present study between mitral and control groups by all methods of comparison justify at least a skeptical attitude toward the assertion that there is a higher frequency of hypertension among persons with mitral stenosis than obtains in the general population. From the evidence presented, nothing can be concluded concerning the effect of hypertension upon the clinical course of mitral stenosis.

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CONGENITAL SUBAORTIC STENOSIS

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THE infrequency of subaortic stenosis is demonstrated by the fact that, since the first report of Chevers,[1] one hundred years ago, only thirty-two cases have been recorded. Our only knowledge of the incidence of this congenital anomaly is based on Maude Abbott's[2] series of 1,000 post-mortem cases of congenital heart disease, in which there were twelve (1.2 per cent) instances of true subaortic (infundibular) stenosis. Inasmuch as no reports on the incidence of this cardiac lesion among the population at large have been presented, the following series of ten cases, discovered during the course of examining approximately 18,000 soldiers, is of interest. Although this results in an incidence of approximately .05 per cent, the frequency of occurrence among the general population is probably somewhat higher, for a certain number of such cases were undoubtedly recognized at various induction centers, and the men consequently rejected for military service. In this respect, therefore, the men examined constitute a selected group.

PATHOLOGY

Grossly, the lesion appears as a firm, raised, fibrous ring of tissue from 1 to 15 mm. below the base of the aortic valve, usually from 2 to 4 mm. in height, and extending 1 to 10 mm. into the ventricular cavity. On microscopic examination, it is seen that this raised band, or shelf, is hyalinized connective tissue covered by intact, flattened endothelium. With Weigert's stain, the fibrous tissue has been shown by Wiglesworth[3] to consist principally of elastic fibers.

Abbott[4] attempted to classify these cases etiologically into two groups, namely, those cases in which the anomaly resulted from a congenital arrest of development, and those in which an early postnatal or late prenatal inflammatory process was considered to be the cause. A mechanical origin has also been postulated,[5] with the belief that the subaortic shelf is produced by the impact of the bloodstream at this area. The most acceptable explanation of the pathogenesis of this lesion is that of Keith,[6] who stated that the raised band represents a remnant or "arrest of atrophy" of the bulbus cordis. Wiglesworth[3] has pointed out that the participation of the endocardial elastica in the formation of the ring corroborates the concept of a congenital origin, and renders doubtful any possibility of an inflammatory or mechanical cause. Walsh, Connerty, and White[7] also think that the lesion is congenital.

CLINICAL DIAGNOSIS

Clinically, the diagnosis of congenital subaortic stenosis is not a difficult one. The patient usually has no symptoms referable to the heart, but auscultation and palpation reveal the murmur and thrill of aortic stenosis, with a normal or nearly normal aortic second sound; the sound is not affected because the lesion does not involve the aortic cusps, but is situated below them. The blood pressure and pulse pressure are normal, and, consequently, the anacrotic pulse of aortic stenosis is not present. With these observations, in the absence of a history of rheumatic fever or suggestive rheumatic attacks in a young patient, the possibility should be suspected. As has been pointed out by Walsh, Connerty, and White,[7] the younger the patient, the more likely will the diagnosis be correct.

If other cardiac defects, congenital or acquired, should be present in addition to the subaortic stenosis, the diagnosis will undoubtedly be more difficult and uncertain. Only two cases of subaortic stenosis with other congenital cardiac defects have been reported,[7, 8] both with bicuspid aortic valves. In only one of these,[7] however, was an aortic diastolic murmur, in addition to the aortic systolic, audible. Apparently, the authors believed that this resulted from the marked degree of deformity of the valve, for, ordinarily, an isolated bicuspid aortic valve produces no auscultatory phenomena.

An unusual number of cases of subaortic stenosis with mitral stenosis have been reported by the French writers.[9-12] These, however, apparently were always of inflammatory origin, probably rheumatic, in which a "fish mouth" mitral valve was accompanied either by an extension of the inflammatory process from the mitral ring to the subaortic endocardium, resulting in the formation of a subaortic shelf (Vulpian, Liouville, and Rendu), or a thickened aortic leaflet of the mitral valve projected below the aortic valve into the ventricular cavity (Lemierre and Bernard). In all cases, the lesion was recognized at post-mortem examination only; the clinical diagnosis had been mitral stenosis, with or without aortic stenosis.

MATERIAL

All the cases were in apparently healthy young men, ranging from 19 to 30 years of age. A careful history revealed no previous attacks of rheumatic fever, epistaxis, frequent sore throats, "growing pains," or erythema. There was no history of syphilis, and serologic tests were negative. Except for two patients who complained of mild to moderate exertional dyspnea (Cases 6 and 7), no cardiac symptoms had ever been present. All had been in the army for periods of two to twelve months, during which time they had been able to perform their duties without difficulty. Only one man had any knowledge of a "heart murmur"

TABLE I

CLINICAL DATA IN TEN CASES OF CONGENITAL SUBAORTIC STENOSIS

CASE NUMBER	AGE (YRS.)	HISTORY OF KNOWN HEART DISEASE	SYMPTOMS	CARDIAC ENLARGEMENT	AORTIC AREA			CAROTIDS		BLOOD PRESSURE
					SYSTOLIC MURMUR	SYSTOLIC THRILL	SECOND SOUND	SYSTOLIC MURMUR	SYSTOLIC THRILL	
1	25	0	0	0	Harsh, rough	0	Normal	Harsh, rough	Slight	118/72
2	30	0	0	0	Moderately loud, rough	0	Normal	Loud, rough	Moderate	115/70
3	21	Known congenital heart disease	0	0	Loud, rough	Slight	Slightly decreased	Loud, rough	Marked	134/82
4	20	0	0	0	Loud, rough	0	Slightly decreased	Louder, rougher	Slight	98/68
5	19	0	0	0	Loud, rough	Slight	Normal	Louder, rougher	Marked	125/78
6	26	0	Dyspnea on exertion	0	Loud, rough	Moderate	Normal	Louder, rougher	Marked	125/84
7	25	0	Dyspnea on exertion	0	Moderately loud, rough	0	Normal	Loud, rough	Moderate	120/82
8	21	0	0	0	Loud, rough	0	Normal	Louder, rougher	Moderate	116/65
9	29	0	0	0	Moderately harsh	0	Normal	Louder, rougher	Slight	130/84
10	20	0	0	0	Moderately loud, rough	0	Slightly decreased	Louder, rougher	Moderate	116/65

prior to the present examination. He had been examined by his private physician before induction, and had been told at that time that he had congenital heart disease.

Clinical examination of these men showed a striking similarity in all; the signs were always consistent with the diagnosis of congenital sub-aortic stenosis. A rough systolic murmur, frequently accompanied by a systolic thrill, was present in the aortic area. On recumbency, both murmur and thrill diminished in intensity, and became more pronounced after full expiration with the patient in the upright position. The murmur was transmitted upward to the carotids, where it usually became louder and rougher. There was minimal transmission of the murmur down along the sternal borders, and in no case was there transmission to the apex or posteriorly to the bases of the lungs. In cases in which no thrill was detectable over the aortic area there was a systolic thrill of slight to moderate intensity and duration over the right carotid artery. In those in which a thrill was palpable over the second intercostal space to the right of the sternum, the intensity and duration were greatly increased in the neck. The aortic first sound was moderately obscured by the murmur, but the aortic second sound was clearly audible, varying from normal to a slight diminution in intensity.

In no case were there murmurs elsewhere, nor was there any other evidence of additional valvular involvement. Regular sinus rhythm was present in all. Unfortunately, radiologic studies could not be made, but, clinically, none of the men showed evidence of cardiac enlargement as ascertained by percussion and the location and thrust of the apical impulse. As would be expected with this type of congenital lesion, the blood pressure and pulse were normal. There was no peripheral clubbing or cyanosis, or evidence of congestive failure.

DISCUSSION

Inasmuch as post-mortem studies have not been made in any of the cases in this series, some doubt may be entertained concerning the validity of the clinical diagnosis. The only other possibility would be acquired aortic stenosis of rheumatic or sclerotic origin. In view of the negative history for rheumatic attacks, the infrequency of isolated rheumatic aortic stenosis at this age, and the absence of other valvular lesions and cardiac enlargement, a rheumatic origin is hardly likely. The age range of the patients is also strongly against the possibility of nonrheumatic, calcific, or sclerotic aortic stenosis. Furthermore, the physical signs (presence of the aortic second sound, normal pulse and blood pressure, Table I) indicate a lesion that does not involve the aortic valve, but must be located proximal to it.

Although this congenital lesion may be compatible with longevity, as evidenced by one of Sternberg's[5] patients, who lived to the age of 77 years, the prognosis in the majority of cases is poor. There is a marked tendency toward the development of bacterial endocarditis,

acute or subacute, at some time within the first three decades of life.[2, 3, 7, 8, 13, 14] Sudden death, with no pathologic changes other than the subaortic ring, has also been reported.[2, 15] In view of this prognosis, accuracy of diagnosis and the rejection of such men for military service become of paramount importance.

SUMMARY AND CONCLUSIONS

Ten cases of congenital subaortic stenosis, discovered during routine examination of approximately 18,000 soldiers, are described; this is an incidence of .05 per cent. Since the prognosis is poor, in that most such patients eventually develop bacterial endocarditis or die suddenly, persons with this disease should be rejected for military service.

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VARICES OF THE BRONCHIAL VEINS AS A SOURCE OF HEMOPTYSIS IN MITRAL STENOSIS

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HEMOPTYSIS, as a complication of rheumatic heart disease, has several unusual features. Stewart[1] defined these clearly. He stressed the blood-streaked sputum, which frequently resembles pure blood. The hemorrhage may exceed 500 c.c. Pulmonary infarction and signs of congestive heart failure are minimal or absent. The hemoptysis may accompany acute exertion, an upper respiratory infection, or auricular fibrillation. All investigators agree that the intrapulmonary blood pressure is elevated. A satisfactory source for the hemoptysis, which would explain all these features, has not been found.

Communications between the pulmonary veins and bronchial veins have been described.[2] Miller[3] demonstrated these communications by injection experiments. We decided to investigate the condition of these communications in cases of mitral stenosis in order to see whether submucous varices were present. Since the bronchial veins are difficult to locate and inject, the injections were made into the pulmonary veins with particulate matter too coarse to enter the capillaries.

PROCEDURE

Lungs fresh from autopsies were injected. The lungs were stored in an icebox overnight to permit loss of rigor, then warmed in an approximately isotonic saline solution to 40° C. before injection. A cannula was inserted into the pulmonary vein from the lower lobe, through which 500 c.c. of warm saline solution were forced to wash out the blood. The injection mass was then introduced through the cannula at a pressure of 80 mm. Hg. This mass was a modification of that originally suggested by Schlesinger[4] for heart injections, and consisted of:

White lead	300 Gm.
Cinnabar	50 Gm.
Sucrose	120 Gm.
Gelatin	70 Gm.
Water	1,000 c.c.

This mixture was fluid at 40° C. The injection pressure was maintained several minutes after immersing the lung in ice water, and then the injected lung was returned to cold storage to allow the mass to harden. Roentgenograms were taken of the first few preparations to check on the completeness of the injection technique, which was found to be satisfactory.

CONTROL CASES

There were seven control cases without clinical signs or pathologic evidence of mitral stenosis. There were six females and one male, aged 26, 39, 47, 59, 59, 62, and 71 years. Three of the patients had hypertension, but only one had terminal cardiac failure in association with uremia. The youngest control was the case of a woman, 26 years of age, who died of a self-administered overdose of barbiturates. The lung showed the same degree of development of bronchopulmonary venous anastomoses and the same pattern of submucosal bronchial veins as the lungs of older patients who died from natural causes. All these cases exhibited similar features.

Fig. 1.

Fig. 2.

Fig. 1.—Typical large bronchus, in the gross, from a 59-year-old, normal woman who died in diabetic coma. There was generalized arteriosclerosis but no cardiac failure. No injected veins are seen, but longitudinal mucosal folds are visible. A, Bronchial folds.

Fig. 2.—Small bronchus from a 26-year-old, normal woman who died from an overdose of sedatives. Note the injected bronchial veins, some forming spider-like patterns and others with no definite arrangement. A and B, Spider-like pattern of the bronchial veins.

In the gross, the bronchial veins, filled with the injected mass, appeared as orange lines in the bronchial mucosa of the smaller and medium-sized bronchi. These veins were conspicuous, and either formed irregular spider-like patterns or had no regular arrangement. Few or no vessels were visible in the larger bronchi. Figs. 1 and 2 show typical large and small bronchi in the gross.

Many very small injected vessels were seen microscopically in the bronchial submucosa. The larger vessels were deeper in the submucosa and were well separated from the lumen of the bronchus. In the spaces between the cartilaginous plates there were larger and more deeply-placed vessels. These seemed to connect the bronchial and pulmonary veins. In the smaller bronchi, the submucosa was thinner and the veins were more superficially placed, making them more conspicuous in the gross (Figs. 3 and 4).
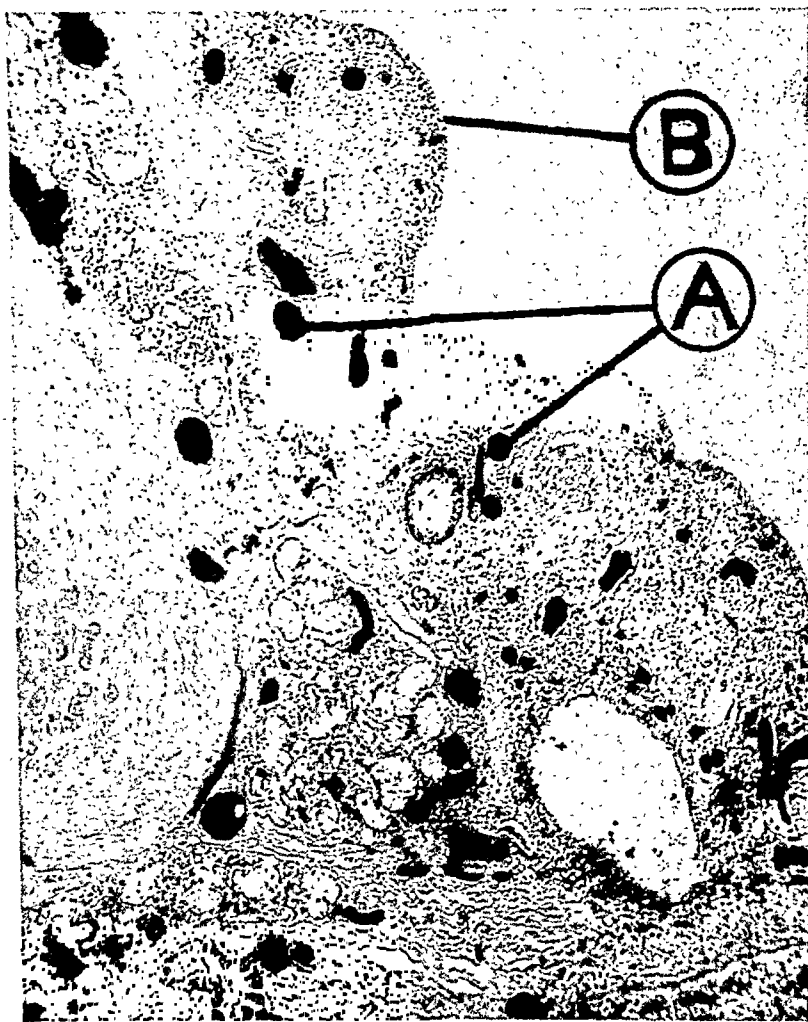
Fig. 3.—Section of a large bronchus from a 62-year-old woman, showing the injected bronchial veins (solid black areas). Note the mucosal fold often seen in the gross. (×90.) A, Injected bronchial veins. B, A mucosal fold.

The injected material was also seen in the veins of the parenchyma of the lung. It did not appear in the pulmonary arteries and capillaries, nor in the bronchial arteries and capillaries. The particles of mercuric and lead salts did not enter channels less than 20 microns in diameter.

NONRHEUMATIC CARDIAC CASES

There were six cases of cardiac failure in this group. The ages of the patients were 39, 53, 57, 58, 63, and 71 years. Four of the patients

had marked hypertension, with cardiac failure. The 58-year-old patient had syphilitic heart disease and aortic insufficiency. He died of congestive heart failure. At autopsy there was syphilitic involvement of the coronary ostia. The sixth patient, aged 63 years, an alcoholic, died of congestive failure. The heart weighed 790 grams, and there were mural thrombi in the right auricle and left ventricle. There was no evidence of coronary occlusion, and the possibility of beriberi heart disease was considered.

Fig. 4.—Section of a smaller bronchus from the same case as Fig. 3. The mucosa is thinner and the veins are more superficial, although of the same size as in the large bronchi. (×90.)

Three of these patients showed slight dilatation of the bronchial veins in the larger bronchi. The veins were definitely more conspicuous than in the normal controls. Fig. 5 demonstrates these changes. The photograph was made from the 39-year-old patient who suffered from arteriolar nephrosclerosis and hypertension. He had coughed up 60 c.c. of frank blood two days before death. The lungs showed some small scattered areas of consolidation in both lower lobes, but no areas of infarction. The bronchial mucosa was markedly hyperemic.

MITRAL STENOSIS CASES

The patients in this group had histories suggestive of rheumatic heart disease, and autopsy reports confirmed the diagnosis of mitral stenosis. Eleven such cases were studied. In six there was some evidence of dilated venous channels, in four of which there were innumerable, wide venous channels running parallel to the lumen in the secondary and tertiary bronchi and disappearing in the main bronchus. A few important details are summarized as follows:
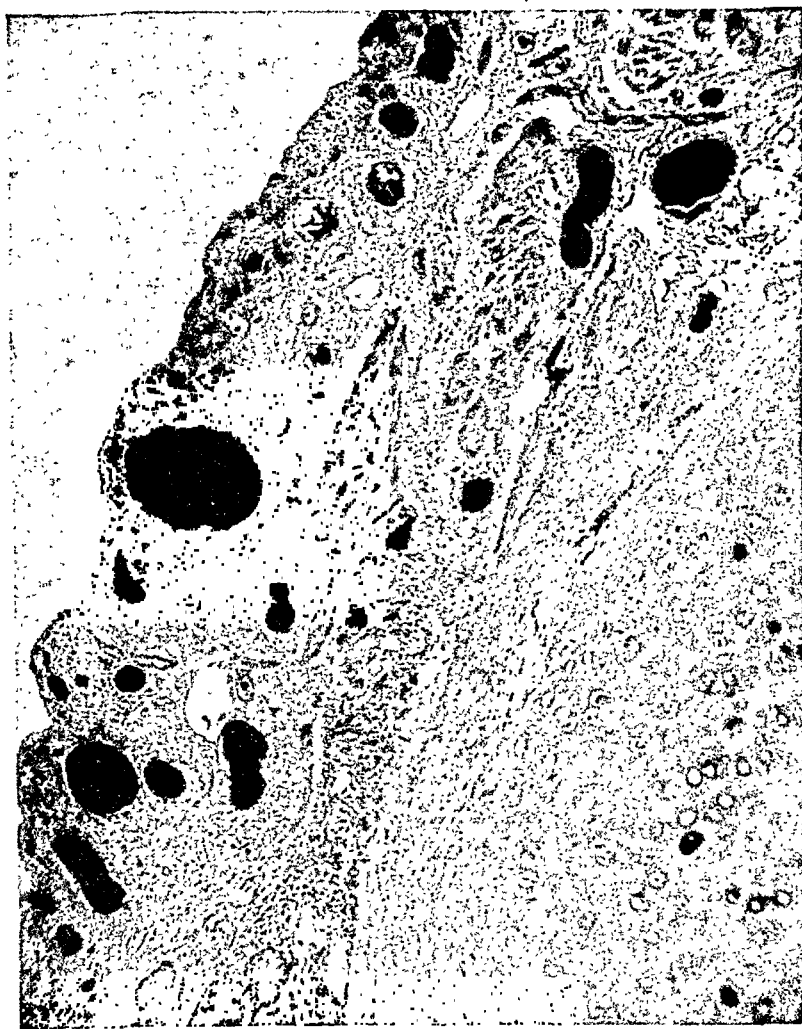
Fig. 5.—Section from a large bronchus from a 39-year-old patient who died of congestive heart failure as a result of long-standing hypertension and arteriosclerosis. Hemoptysis (60 c.c.) occurred twenty-four hours before death. The dilated bronchial veins may be seen as large black areas just beneath the surface of the bronchial mucosa.

CASE 1.—A 33-year-old woman had had chorea and joint pains at the age of 6 years. Mitral stenosis was diagnosed at that time. She was hospitalized eleven times thereafter. Auricular fibrillation had been present for fifteen years. Her first hemoptysis occurred nine years before death. On her last admission there were signs of advanced cardiac failure. Autopsy showed involvement of the mitral, tricuspid, and aortic valves. The left auricle comprised one-half the volume of the heart. The veins of the visceral pleura were dilated and anastomosed with dilated veins in the diaphragm. The injected specimen showed numerous dilated, tortuous bronchial veins in the larger bronchi.

CASE 2.—A 16-year-old girl was first found to have an enlarged heart and systolic and diastolic murmurs at the age of 7 years. Dyspnea gradually increased during the next seven years. At the age of 15 years she became acutely decompensated. The only hemoptysis occurred the day before death. Normal sinus rhythm was present. She died of cardiac failure. Autopsy revealed cardiac hypertrophy, myocarditis, mitral stenosis, and thrombi in both auricles. There was definite pulmonary arteriosclerosis, and there were thrombi in the pulmonary arteries, with infarcts. Marked varices of the bronchial veins in the larger bronchi were found on injection (Figs. 6 and 7).

Fig. 6.—The large bronchi from a 16-year-old girl with mitral stenosis (Patient D.M.). The dilated bronchial veins are seen, along with some mucosal folds. The veins stream toward the hilum, forming a collateral circulation. A, Dilated bronchial veins. B, Mucosal fold.

CASE 3.—A 33-year-old woman had rheumatic fever in childhood. At the age of 23 years she first noticed attacks of tachycardia, and, four years later, dyspnea became pronounced. Five months before death hemoptysis occurred. There were physical signs of mitral stenosis and insufficiency and auricular fibrillation. She developed an acute terminal pneumonia. The autopsy diagnosis was mitral stenosis and insufficiency, hemorrhagic bronchitis, and pulmonary congestion. Because of the acute hemorrhagic bronchitis it was impossible to see any dilated bronchial veins in the injected specimen.

CASE 4.—This 37-year-old patient had her first attack of rheumatism at the age of 12 years. There were no cardiac symptoms until the age of 38 years, during her pregnancy, when she developed mild cardiac failure. There was no history of hemoptysis. She was admitted with signs of acute rheumatic heart disease, mitral stenosis and insufficiency, and normal sinus rhythm. Autopsy revealed a large heart and mitral stenosis and insufficiency, with calcification of the leaflets. There were a few large infarcts in the lungs. The injected specimen showed fine, linear veins in the mucosa of the larger bronchi.

Fig. 7.—Section of a large bronchus from the same case as Fig. 6. Note the great dilatation of the bronchial veins and their situation close to the lumen of the bronchus. (×90.)

CASE 5.—This girl was 27 years of age. Four years previously she was told she had heart disease. She was admitted with subacute bacterial endocarditis. There were signs of mitral stenosis and insufficiency and aortic stenosis and insufficiency, with normal sinus rhythm. Autopsy confirmed this diagnosis. There were no pulmonary infarcts. The injected specimen showed enlarged, slightly tortuous, longitudinally arranged veins near the bifurcation of the larger bronchi.

CASE 6.—This 30-year-old woman had rheumatic fever and chorea at the age of 7 years. Rheumatic heart disease was diagnosed six years before death. She died, in her eighth month of pregnancy, of acute

pulmonary edema. There was no history of hemoptysis. The heart rhythm was regular. Autopsy revealed aortic stenosis and insufficiency, with only moderate evidence of mitral stenosis. The injected lung specimen revealed only slight dilatation of the bronchial veins in the major bronchi.

CASE 7.—This 31-year-old man had attacks of rheumatic fever at the ages of 8 and 13 years. There was no history of hemoptysis. He was admitted to the hospital in congestive heart failure, with signs of both aortic and mitral valve involvement and normal rhythm. Autopsy confirmed the diagnosis of the valvular lesions. The injected specimen revealed marked injection and dilatation of the bronchial veins. The veins were numerous and tortuous, and streamed toward the hilum of the lung.

CASE 8.—This patient was a 42-year-old housewife. There was no history of rheumatic fever, but, at the age of 36 years, she was told she had heart disease. There was no history of hemoptysis. The heart was enlarged and there were signs of mitral stenosis and insufficiency and auricular fibrillation. She died of congestive heart failure, accompanied by bronchopneumonia. At autopsy the mitral valve was typically "buttonhole" in character. The injected specimen revealed no dilatation of the bronchial veins, and microscopic sections showed only moderately dilated veins deep in the bronchial mucosa.

CASE 9.—This 52-year-old woman died of pulmonary infarction and rheumatic heart disease. There was no history of hemoptysis preceding her terminal illness. Autopsy revealed definite mitral stenosis and thickening of the leaflets of the aortic valve. The injected lung specimen showed no evidence of dilated veins.

CASE 10.—This man was a 56-year-old hypertensive patient with mitral stenosis and insufficiency and auricular fibrillation. Autopsy confirmed the diagnosis of mitral stenosis, and there was also pulmonary arteriosclerosis. There was no definite dilatation of the bronchial veins in the injected specimen.

CASE 11.—This patient was 57 years old. Symptoms of decreasing cardiac reserve had been present over a period of four years. Three weeks before admission he had hemoptysis and pain in the chest. Auricular fibrillation was present, and autopsy revealed mitral stenosis and insufficiency, with a dilated left auricle. There was no evidence of pulmonary infarction. The pulmonary arteries showed marked arteriosclerosis. The injected specimen showed many anastomotic vessels in the bronchial mucosa, and the sections revealed large, dilated bronchial veins which lifted the mucosa into the lumen of the bronchus.

Four of these patients had hemoptysis at some time, but in only one case could it be correlated with pulmonary infarction. A marked hemorrhagic bronchitis was present in Case 3, and it was impossible to detect the presence of dilated veins. Six of the eleven patients showed definite evidence of enlarged bronchial veins. Four of these six patients showed greatly dilated bronchial veins along the longitudinal axis of the large bronchi. They were fairly straight and parallel, and seemed to stream toward the main bronchus. Fig. 6 shows a photograph of a large bronchus from Case 2. The large mucosal folds

are visible, as well as the innumerable dilated veins on the surface of the mucosa. Fig. 7 is a section of one of the bronchi, showing the injected bronchial veins lying just under the mucosal surface.

Fig. 8.—Section of a large bronchus from a 56-year-old man with mitral stenosis, but no history of hemoptysis (Patient G.Z.). The bronchial veins are somewhat enlarged, but not very superficial. (×90.)

DISCUSSION

Most authorities seem to agree that there are only capillary anastomoses between the pulmonary and bronchial circulations. Wiggers[5] states that there are no functional arterial or venous anastomoses. Wood, Crever, and Miller[6] and Daly[7] also state that there are only connecting capillaries on the arterial side. In another article, Berry and Daly[8] indicated the further possibility of small arteriole or venule connections. The injection mass which we employed was never seen in the pulmonary capillaries, and it did not appear in the bronchial or pulmonary arteries. The smallest vessels filled with the mass measured approximately 20 microns in diameter. However, the injected material passed freely, even in the control cases, from the pulmonary to the bronchial veins. The injection pressure used (80 mm. Hg) might have been high enough to dilate capillary anastomoses. This seems

unlikely because the injection mass did not enter the capillaries in the parenchyma of the lung. There must be innumerable venules anastomosing the bronchial and pulmonary venous beds, both in normal lungs and in cases of heart failure.

Whatever the type of anastomosis, the blood flow through it is thought to be from the bronchial to the pulmonary circulations, according to Miller,[2] Berry and Daly,[5] and others, although there are no data on normal, left auricular pressures in man. We believe that when mitral stenosis is interposed, the flow to the left auricle through the pulmonary veins is hindered, and the pressure in these veins rises above that in the right auricle. The blood flow through the anastomosis is reversed, and the blood passes from the pulmonary circulation into the bronchial veins and back to the right side of the heart, via the azygos, hemiazygos, and intercostal veins. The submucosal bronchial veins leading toward the main bronchi dilate greatly to handle this collateral flow, and even become grossly visible. The hemoptysis which often accompanies mitral stenosis, yet is not associated with acute pulmonary edema or pulmonary infarction, is probably caused by the rupture or ulceration of these engorged bronchial veins. This hemoptysis resembles massive bleeding from hemorrhoids and esophageal varices, which, like the bronchial veins, are submucous shunts between large venous drainage areas. A severe coughing spell, mild ulcerative bronchitis, or a rise in left auricular pressure could initiate such attacks of hemoptysis.

This view differs widely from the explanations previously offered. The most frequently suggested opinion was that the extreme congestion and hypertension of the pulmonary arterial and venous bed eventually caused these vessels to rupture. A long list of writers, including White,[9] McKenzie,[10] Vaquez,[11] Stewart,[1] and Ginsberg,[12] have held this opinion, which implies simply an accentuation of the diapedesis of erythrocytes into the alveoli in heart failure. Wolff and Levine[13] suggested this same cause, but felt that sclerosis of the vessels might be a necessary precursor of the hemorrhage. As Brenner[14] pointed out, pulmonary arteriosclerosis frequently does accompany mitral stenosis. However, two of our four patients with hemoptysis showed no evidence of pulmonary sclerosis. Proft, as quoted by Oppenheimer and Schwartz,[15] explained the hemoptysis as due to sudden dilatation of the lung capillaries, with diapedesis into the alveoli, or to dilatation with rupture of the capillaries lining the small bronchioles. It does not seem likely that diapedesis into the alveoli could account for the sudden profuse hemorrhages which often occur. In all of our cases of mitral stenosis there were "heart failure" cells in the alveoli. Only one of our four patients with hemoptysis had gross areas of bleeding, resembling infarcts, in the lung parenchyma. The vessels of the smallest bronchi and bronchioles did not differ from the normal. For this

reason it does not seem likely that the bleeding arises from the small vessels in the bronchiolar system.

Estimates of the actual incidence of pulmonary hemorrhage in mitral stenosis range from Wolff and Levine's 10 per cent[13] to Hay and Hunt's 23 per cent.[16] Hemoptysis in mitral stenosis has long been recognized as a poor prognostic sign (Wolff and Levine[13]). The bleeding, per se, is not dangerous. However, it is the result of long-standing and marked mitral stenosis. Hence, the hemorrhage indicates a very poor cardiac status and is correlated with a poor prognosis. Our four patients with hemoptysis lived one day, four weeks, three months, and nine years, respectively, after their initial pulmonary hemorrhage. The patient (Case 1) who lived nine years had the most marked evidence of collateral bronchial venous flow, and a collateral circulation had also been set up through the veins of the diaphragm.

Age has no effect upon the normal capacity of the bronchial veins. Our seven controls ranged in age from 26 to 71, and there were no observable differences in the size of their vessels. The oldest of our mitral stenosis patients was 57, and the youngest, 16 years. Hemoptysis occurred in both of these and in two other patients at the age of 33 years, so that this bleeding shows no age relationships. Hypertension also does not appear to affect the normal capacity of the bronchial veins unless chronic congestive heart failure occurs. There were no changes in the bronchial veins in any of the normal controls, and coronary and pulmonary arteriosclerosis did not affect the flow through the bronchial veins when it occurred in the patients.

SUMMARY

1. A method for injecting the bronchial veins is described.

2. This method indicates the presence of direct venous connections between the bronchial and pulmonary veins in men of all ages.

3. Mitral stenosis causes dilatation of the bronchial veins in the submucosa of the larger bronchi as a result of the establishment of a collateral flow through them.

4. In cases of mitral stenosis in which infarction and acute pulmonary edema are not present, hemoptysis is probably due to bleeding from these dilated veins.

5. Age, hypertension, and arteriosclerosis do not affect the bronchial venous bed, but some dilatation occurs in chronic congestive heart failure of long standing, although the only lesion of the mitral valve may be dilatation of the valve ring.

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THE ASSOCIATION OF PAROXYSMAL ATRIAL TACHYCARDIA WITH ATRIAL FLUTTER OR FIBRILLATION

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IN A RECENT study of our cases of paroxysmal atrial tachycardia in which A-V block was present,[1] we were surprised to note the not infrequent association of paroxysmal tachycardia with atrial flutter or fibrillation. Although it is well recognized that flutter and fibrillation are frequently associated, and probably are manifestations of mechanisms which are fundamentally the same, it has been generally felt that paroxysmal atrial tachycardia is different, specifically and generically, and bears no relationship whatsoever to a circus mechanism. Without attempting to discuss the fundamental nature of any of these three disturbances of the cardiac mechanism, we wish to show in this communication that this type of paroxysmal tachycardia with A-V block is more intimately associated with flutter and/or fibrillation than has hitherto been appreciated.

Existing evidence on this point is scanty. Hirschfelder,[2] in experiments employing faradism of the auricular appendage of the dog, found that stimuli of low or moderate intensity gave rise to paroxysmal tachycardia, whereas intense and prolonged stimulation produced auricular fibrillation. This led him to conclude that "true paroxysmal tachycardia is usually caused by increased irritability of the heart muscle, especially of the auricles, which probably pass into a state of fibrillation." This possibility was denied by Lewis,[3] although he described in great detail a case[4] in which a short period of fibrillation was recorded during an atrial paroxysm. He also noted the fact, which must have been apparent to many, that atrial premature beats commonly precede the ultimate appearance of either paroxysmal tachycardia or fibrillation. Also, in experimental animals, rapid, rhythmic stimulation of the auricle simulated tachycardia, whereas increased rates of stimulation produced flutter or fibrillation.[5]

In 1932, Carr[6] reported a unique instance of paroxysmal tachycardia, apparently of A-V nodal origin, in which short periods of atrial flutter interrupted the paroxysms. On a single occasion, pressure on the right carotid sheath resulted in a shift from paroxysmal tachycardia to flutter with high-grade A-V block. After the administration of $1/100$ grain of atropine subcutaneously, the tachycardia changed within one minute to

flutter; this was soon followed by sinus rhythm with frequent atrial premature beats, and short atrial paroxysms appeared later.

Brown[7] has also recorded a single case in which paroxysmal atrial tachycardia was closely associated with a circus movement. His patient was overdigitalized, and, as a result, A-V block appeared, and the mechanism was shortly converted to fibrillation. Because of the A-V block, the electrocardiograms had been thought by some to represent atrial flutter rather than tachycardia, and Brown resorted to esophageal leads to make the differentiation clear.

Recently, Barker, et al.,[8] have described eighteen examples of paroxysmal tachycardia with A-V block. Among this group there were three patients who also showed flutter or fibrillation. They state that, of 100 cases of paroxysmal atrial tachycardia, in only five was the patient known to have had flutter or fibrillation also; in three of the five, partial A-V block was present during the tachycardia. In their Case 2, flutter was first seen; four days later atrial tachycardia was recorded, and it is worth noting that, in the interim, 0.85 Gm. of digitalis had been administered intravenously. The further injection of 0.35 Gm. of digitalis produced 2:1 A-V block. Digitalis was continued by mouth, and the tachycardia with block persisted. Two months later there was normal sinus rhythm, and this appeared to persist. After ten months more, an electrocardiogram showed flutter in the first two leads and fibrillation in the third lead.

In Case 10 of Barker, et al., atrial tachycardia with A-V block was thought to have been due to excessive digitalization. Two days later atrial fibrillation was recorded. Case 12 showed a similar transition. This patient had been taking digitalis for three years. The day after admission he was given an additional 0.5 Gm., and the tracing taken the following day showed atrial paroxysmal tachycardia with A-V block. Two days later atrial fibrillation was present. The apparent role played by overdigitalization in these three cases, both in producing the tachycardia and in producing block, agrees with our own experience[1] in this connection.

Two additional cases have been reported which have been interpreted by the authors as illustrating the conversion of paroxysmal tachycardia to flutter. It is necessary at this point to recall the fact that there appears to be only one clear criterion for the differentiation of tachycardia and flutter, i.e., the presence or absence of a continuous atrial circus mechanism, as indicated by the absence or presence of an isoelectric period in the electrocardiogram. When an isoelectric period is found it indicates that continuous electrical activity of the atrium, due to a circus movement, is not present. Parkinson and Mathias[9] have recorded a remarkable case of paroxysmal tachycardia in which there was a cyclic variation in the atrial rate. As the rate rose from 155 to about 225 per minute, A-V block obviously developed. The authors

took this to mean that flutter had replaced the tachycardia, but our own opinion of the tracings would indicate merely that A-V block had developed during the time when the atrial rate was most rapid. We have reported similar cases.[1]

The impression has hitherto been current that A-V block was in itself prima-facie evidence that flutter was present rather than tachycardia. The paper of Barker, et al.,[8] and our report[1] should dispel this impression. Geraudel[10] has apparently fallen into this same error, and has gone so far as to deny the very existence of paroxysmal tachycardia, and to say that all such cases are flutter with 1:1 A-V conduction.

MATERIAL

Most of the cases cited were found during our previous study of A-V block in tachycardia. A few were not included at that time because of uncertainty as to their true interpretation. When we noted the high incidence of flutter or fibrillation among cases of tachycardia with block, we confidently expected to discover many more examples of such association among the more numerous cases of tachycardia without A-V block. In this anticipation we were disappointed; only two additional cases were forthcoming, thus amply confirming the similar experience of Barker and his associates. In one of them, the association was not intimate (Case 1); in the other (Case 13), fibrillation immediately followed the termination of a typical attack of tachycardia. Tabulation (Table I) of all of our cases shows that flutter, or fibrillation, is ten times more likely to be found in those cases of paroxysmal tachycardia in which there is A-V block than it is when such block is absent.

TABLE I

CASES OF SUPRAVENTRICULAR PAROXYSMAL TACHYCARDIA

ATRIOVENTRICULAR BLOCK		ASSOCIATION WITH FLUTTER OR FIBRILLATION	
		PRESENT	ABSENT
Present	42 cases	12 (28.6%)	30
Absent	70	2 (2.86%)	68
	112	14	98

CASE REPORTS

CASE 1.—J. R., a white woman, aged 33 years, John Sealy Hospital No. 19452, had been under observation since 1926 because of rheumatic heart disease with mitral stenosis. Palpitation and precordial pain had been the chief symptoms of cardiac origin. The first electrocardiogram taken on this patient was during an attack of paroxysmal tachycardia on Sept. 6, 1932 (Fig. 1, A). The next day sinus rhythm was present, with a normal P wave. She was admitted to the hospital again in October, 1932, and was found to have acute fibrinous pericarditis. Frequent atrial premature beats were noted in many tracings. Digitalization was begun on Dec. 13, and stopped on Jan. 15, 1933. On January 17, she was observed in a paroxysm of

tachycardia, rate 160 per minute, which was stopped by carotid sinus pressure; the rate fell immediately to 60 per minute. On January 19, atrial fibrillation was recorded (Fig. 1, *B*). Again, on January 21, a paroxysm of tachycardia was stopped by pressure over the carotid sinus; on January 23 she was fibrillating again. During several succeeding years there were numerous atrial premature beats. In April, 1938, hydrops of the gall bladder was drained; postoperatively, fibrillation appeared, and was controlled by digitalis. After the withdrawal of digitalis the sinus pacemaker spontaneously resumed its role. Later in 1938, during an attack of bronchopneumonia, atrial fibrillation was present for a few days, but disappeared spontaneously.

CASE 2.—A. D., a white girl, aged 14 years, John Sealy Hospital No. 66298, entered the hospital April 17, 1940. For four years she had had attacks of dyspnea associated with tachycardia, vertigo, and pain in the chest. The heart rate was found to be 188 per minute; the blood pressure was 78/56. Quinidine was given on April 19 and again on April 21. On April 24, digitalization was begun, and by April 28 the dosage was reduced to 1½ grains daily, at which level it was held during the remainder of her stay in the hospital. Electrocardiograms taken during the ten days after admission showed gradual slowing of the heart rate, but with persistence of the abnormal P wave (Fig. 2, *A*). In spite of the atrial slowing, partial A-V block with dropped beats was noted first on April 26, and was found in tracings taken at intervals until May 2. On May 16, an attack of tachycardia developed, with a heart rate of 250 per minute. Carotid sinus pressure, ocular pressure, vomiting induced by ipecac, acetyl-β-methylcholine, and quinidine were used, but produced only transient slowing of the heart, and death occurred late that day. We cannot be certain that this final attack was one of atrial flutter (Fig. 2, *B*), but the case is included because this seems to be a likely electrocardiographic, as well as clinical, diagnosis, for the bizarre P waves were no longer present, and carotid sinus pressure produced transient slowing. Unfortunately, no curves were obtained during any of the brief periods of cardiac slowing.

Necropsy showed an enlarged heart, weighing 530 grams. The ductus arteriosus was patent, and there was congenital hypoplasia of the aorta.

CASE 3.—K. L., a white man, aged 45 years, John Sealy Hospital No. 57248, was admitted March 7, 1939, in congestive heart failure; the blood pressure was 252/168. Lumbar sympathectomy had been performed fourteen months previously in an effort to relieve this marked hypertension, but no benefit had resulted. In the five days before this admission, the patient had taken 15 tablets of digitalis leaf, each of 1½ grains. On March 13, before 2.5 mg. of digoxin were given intravenously, sinus tachycardia was present; the next day, atrial fibrillation was recorded (Fig. 3, *A*). On March 17, sinus rhythm was present again (Fig. 3, *B*). On that day, and again on March 18 and 19, 3 grains of digitalis were given each day. On March 20, paroxysmal atrial tachycardia was present, with partial A-V block (Fig. 3, *C*). Digitalis was given again two days later, and the paroxysmal tachycardia recurred; it was still present on March 27.

During this period renal insufficiency had become progressively more severe, and the patient died in uremia on March 29. At necropsy the heart weighed 670 grams; there were marked nephrosclerosis and a few atheromatous plaques in the aorta.
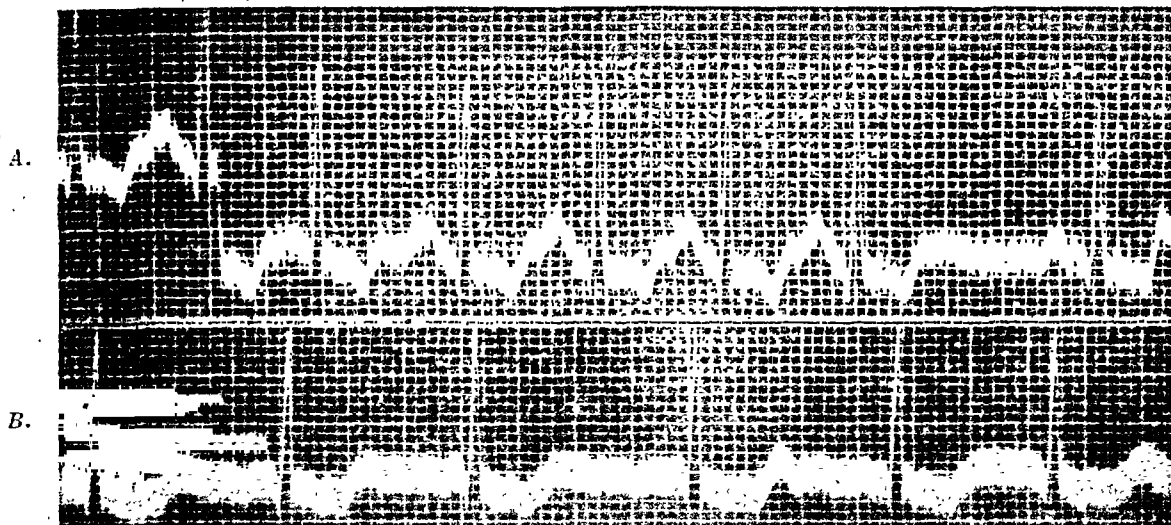
Fig. 1.—Case 1. *A*, Lead II; the termination of a paroxysm of atrial tachycardia recorded on Sept. 6, 1932. *B*, Lead II; atrial fibrillation, Jan. 19, 1933.
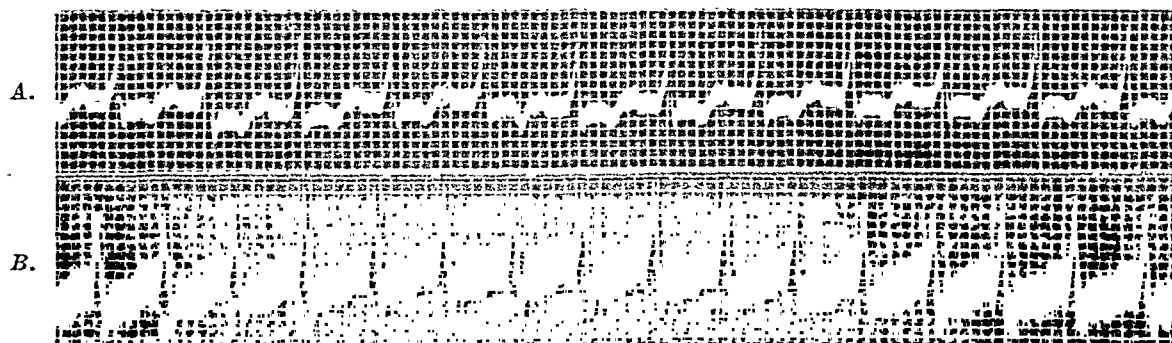
Fig. 2.—Case 2. *A*, Lead II; paroxysmal atrial tachycardia, April 17, 1940. *B*, Lead II; taken during terminal attack of tachycardia, May 16, 1940; probably atrial flutter.
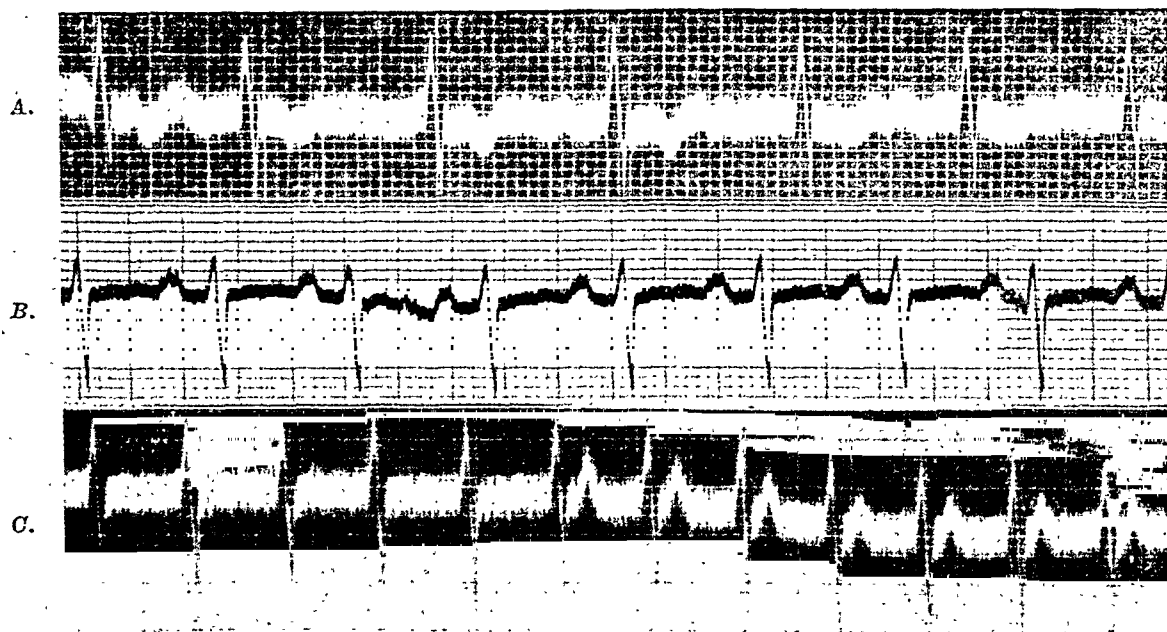
Fig. 3.—Case 3. *A*, Lead II; showing atrial fibrillation on March 14, 1939. *B*, Lead II; sinus rhythm on March 17. *C*, Lead II on March 20; paroxysmal atrial tachycardia; partial A-V block was apparent in parts of the curve.

CASE 4.—T. R., a white man, aged 49 years, John Sealy Hospital No. 66787, entered the hospital Oct. 15, 1940. He had been seen on several previous occasions because of hypertensive heart disease with congestive heart failure, and on this admission he presented the usual manifestations of this condition.

In the period from October 22 to December 1, he received 3.2 Gm. of digitalis leaf. On December 1 he was given 2 c.c. of mercupurin intravenously. Atrial fibrillation was present the next day (Fig. 4, A), but was replaced by sinus rhythm after 18 grains of quinidine. The following day, December 3, paroxysmal atrial tachycardia was found, at a rate of 182 per minute, with partial A-V block (Fig. 4, B). The ectopic pacemaker still controlled the atria on December 4, although the rate had dropped to 135 per minute. Sinus rhythm then reappeared.

Death occurred on December 14. Necropsy showed a heart weighing 600 grams, with only slight coronary arteriosclerosis. Ante-mortem thrombi were present in the right atrium and in both ventricles, and there were multiple pulmonary infarcts. There were the usual evidences of nephrosclerosis and chronic passive congestion.

CASE 5.—E. S., a colored woman, aged 68 years, John Sealy Hospital No. 75227, had been hospitalized in March and again in August, 1942, for hypertensive and arteriosclerotic heart disease in the stage of congestive heart failure. The electrocardiograms taken during this time showed numerous supraventricular premature beats, and the first tracing recorded during the August admission showed atrial fibrillation (Fig. 5, A); subsequent ones at this time showed sinus rhythm.

Her last admission was on March 25, 1943, when she had a recurrence of severe congestive heart failure in spite of the fact that for the preceding three weeks she had been taking 0.3 Gm. of digitalis leaf daily. Nausea and vomiting had appeared before entrance to the hospital. The electrocardiograms taken March 26 showed a basic sinus rhythm, but with many short runs of atrial premature beats (Fig. 5, B). On March 29 the pulse rate was counted at 170 per minute. The electrocardiograms taken that day showed atrial flutter with 2:1 A-V block (Fig. 5, C); this same mechanism was found again on March 31. On this day, two 5-grain doses of quinidine were given. On April 1 the flutter had disappeared, and there was again a sinus rhythm with frequent short runs of atrial premature beats; six doses of quinidine were given, but the numerous extrasystoles persisted. During the remainder of her stay in the hospital she was given 5-grain doses of quinidine three times daily. The short paroxysms of atrial tachycardia (Fig. 5, D) persisted until her death, April 18. The rate of the ectopic focus was highly variable; occasionally partial A-V block appeared, with dropped ventricular beats.

CASE 6.—F. G., a colored man, aged 50 years, John Sealy Hospital No. 10629, was admitted Jan. 20, 1942. Hypertensive and arteriosclerotic heart disease had been diagnosed twelve years previously, and for six years exertion had caused dyspnea. During a previous admission in October, 1941, atrial fibrillation had been recorded (Fig. 6, A). During the intervening months he had experienced repeated attacks of paroxysmal tachycardia, associated with dyspnea and precordial pain. In the three months preceding the present admission, the patient had taken 0.2 Gm. of digitalis leaf daily. The electrocardiogram taken January 20 showed paroxysmal atrial tachycardia with an atrial rate of 214 per minute. The next day the rate was 200 per minute, with 2:1
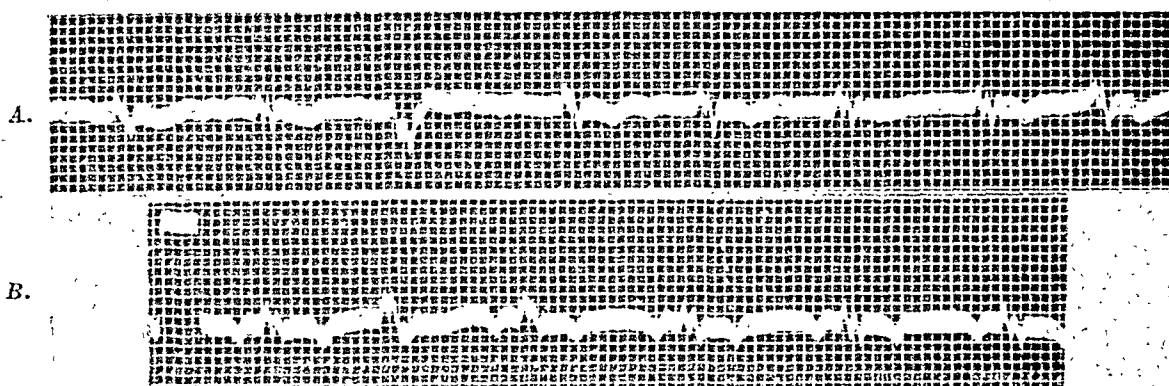
Fig. 4.—Case 4. *A*, Lead II on Dec. 2, 1940; atrial fibrillation. *B*, Lead II on December 3; showing paroxysmal tachycardia with partial A-V block.
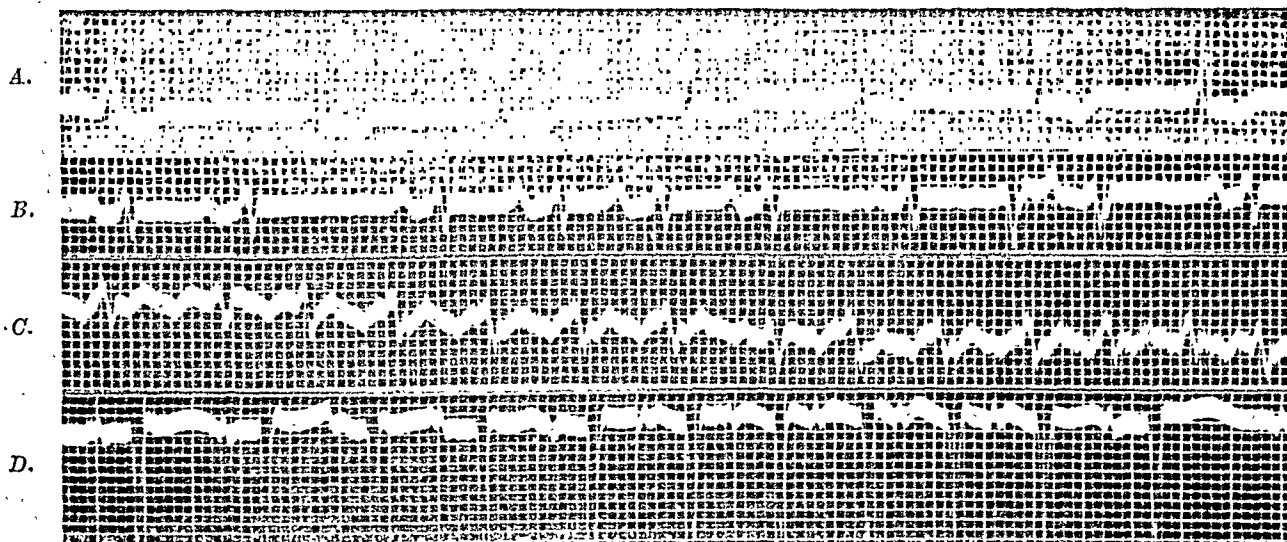
Fig. 5.—Case 5. *A*, Lead I on Aug. 4, 1942; atrial fibrillation. *B*, Lead II on March 26, 1943; showing short runs of atrial premature beats. *C*, March 29, Lead II; atrial flutter. *D*, Lead CF₂ on April 6, 1943; showing a short paroxysm of tachycardia.
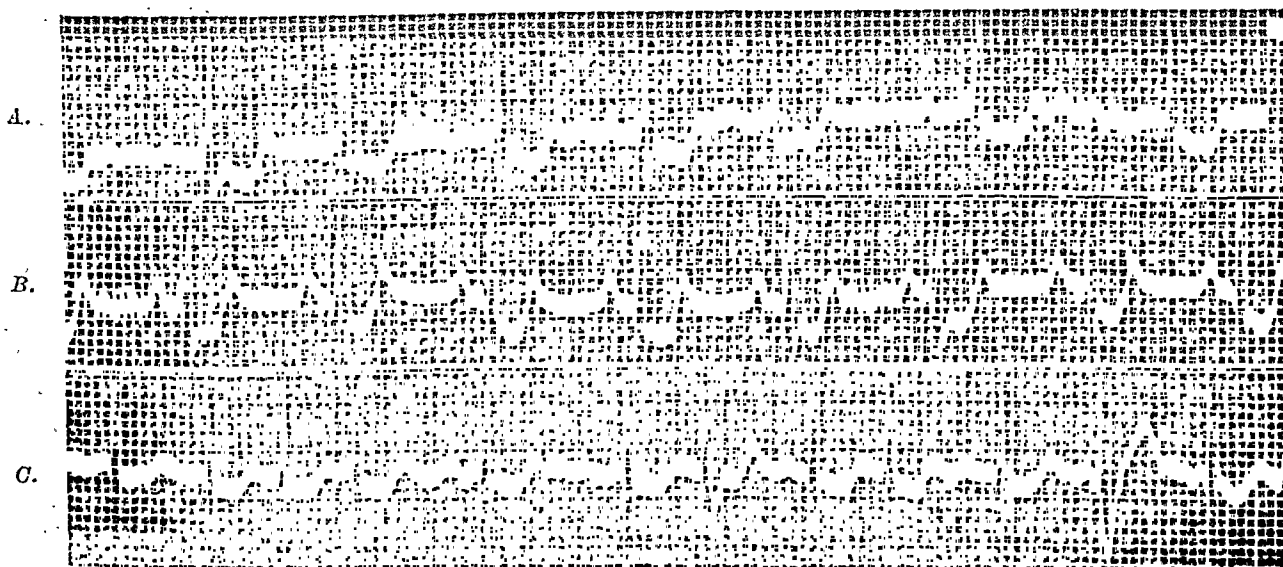
Fig. 6.—Case 6. *A*, Lead II on Oct. 24, 1941; auricular fibrillation. *B*, Lead II, Jan. 21, 1942; paroxysmal atrial tachycardia, with 2:1 A-V block. *C*, Lead II on Oct. 15, 1942; showing a return of fibrillation.

A-V block (Fig. 6, *B*). When the patient sat up there was 1:1 conduction; when he lay down, or when pressure was applied to the carotid sinus, partial block, varying from 2:1 to 4:1, appeared. He was seen again as a clinic patient in October, 1942. At this time atrial fibrillation was again present (Fig. 6, *C*).

CASE 7.—E. V., a white woman, aged 33 years, John Sealy Hospital No. 68211, entered the hospital Oct. 31, 1941. She presented a syndrome characterized by hypertension (174/130), 4 plus proteinuria, generalized edema, pulmonary infarction, and myocardial failure. In June, 1940, she had had a cesarean section, followed by pneumonia and thrombophlebitis. Since then there had frequently been edema of the right leg. Two months before admission she was delivered of a 7½-month-old fetus without complication, although during the pregnancy she had had edema of the ankles and swelling of the eyes. She had orthopnea, a continual cough, and a small amount of pink, frothy sputum.
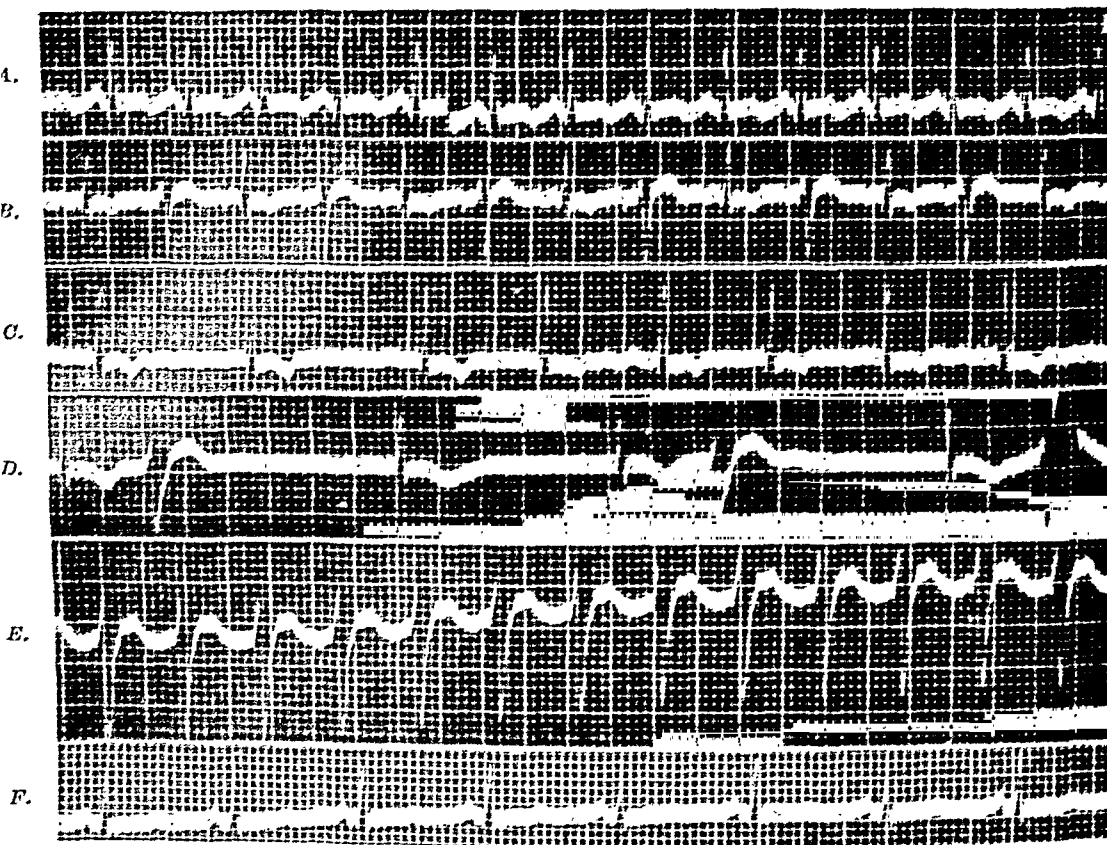
Fig. 7.—Case 7. *A*, Lead I, Oct. 31, 1941; paroxysmal atrial tachycardia. *B*, Lead I, November 4; showing alternation. *C*, Lead I, November 5; atrial fibrillation. *D*, November 11, Lead I; showing persistence of fibrillation. *E*, Lead IVF, also on November 11; showing a short paroxysm of tachycardia. *F*, Sinus rhythm on November 24; Lead I.

The urine showed marked proteinuria, a specific gravity of 1.030, many leucocytes, and a few hyaline and granular casts; erythrocytes were rare. Electrocardiograms taken on the day of admission showed supraventricular tachycardia with an atrial rate of 171 per minute (Fig. 7, *A*). On October 31, 1.5 mg. of digoxin were given, and on the next day 0.5 mg. more was administered. On that day, November 1, the atrial

rate dropped to 136, but the focus was still an ectopic one. From November 1 to 4, 1 Gm. of digitalis leaf was given by mouth. On November 4 the atrial rate was 158 per minute. There was 1:1 A-V conduction, with a P-P interval of 0.38 second. The Q-Q interval, however, alternated between 0.37 and 0.39 second, with QRS alternation and a P-R interval alternating between 0.12 and 0.14 second (Fig. 7, B). On November 2, 5 grains of quinidine were given by mouth every hour for seven doses without terminating this attack. On November 5 the mechanism had changed to atrial fibrillation (Fig. 7, C), and this persisted until November 24. The atrial tachycardia recurred at the rate of 160 per minute on November 9; magnesium sulphate, by vein, injected for the purpose of measuring the circulation time, stopped the tachycardia immediately.
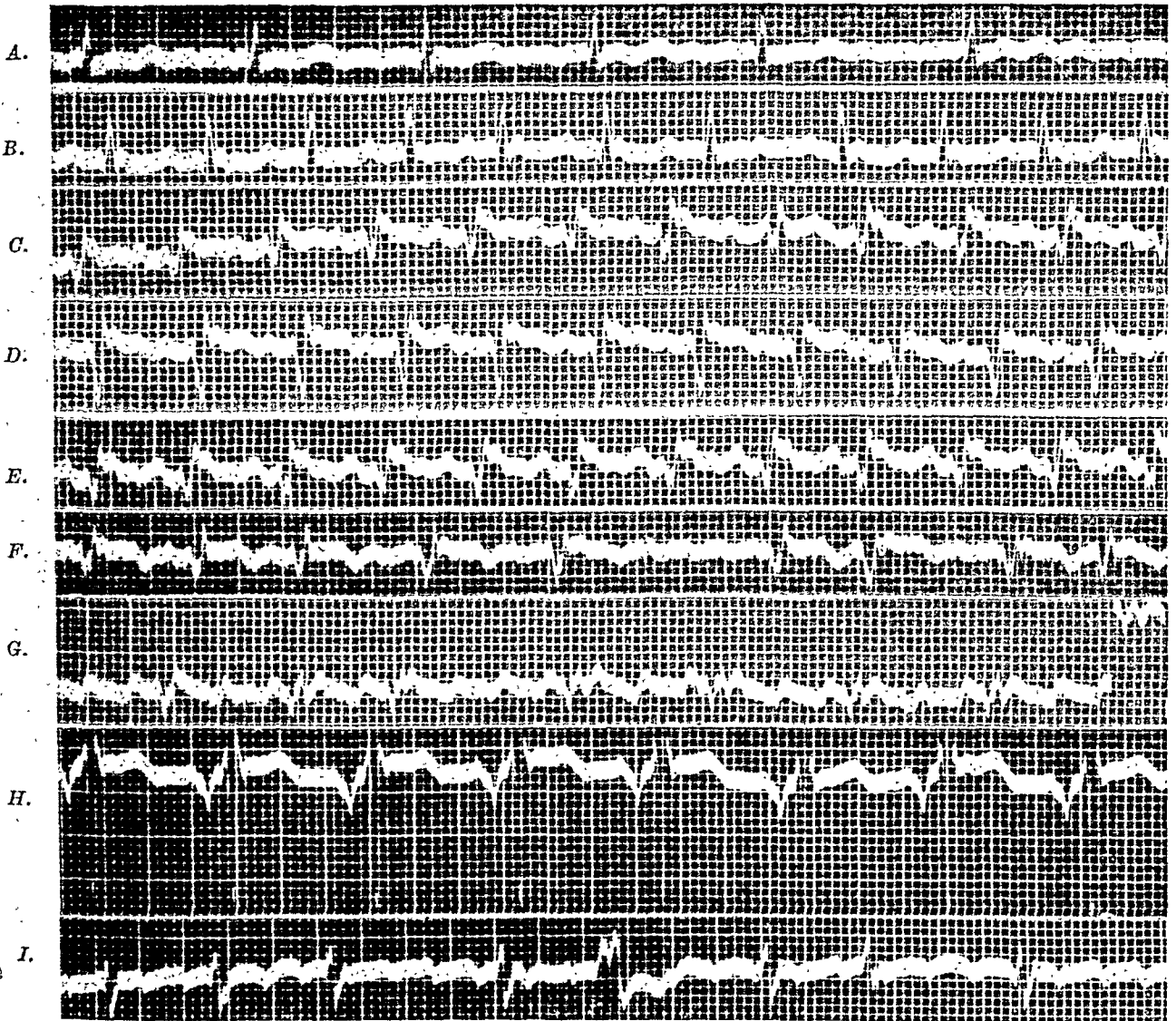
Fig. 8.—Case 8. A, Lead II; atrial fibrillation on Feb. 2, 1943. B, C, and D, Leads I, II, III, taken on February 19; showing atrial tachycardia with 2:1 A-V block. E, Lead II, February 20, 10:00 A.M.; tachycardia. F, Lead II, February 20, noon; fibrillation or impure flutter. G, Lead II, February 22, 9:30 A.M.; flutter. H, February 22, 4:00 P.M.; esophageal lead, sinus rhythm. I, February 23, Lead CF1; impure flutter or fibrillation again.

On November 11, atrial fibrillation was still present (Fig. 7, D), although while taking an electrocardiogram one lead showed a short paroxysm of tachycardia (Fig. 7, E). Digitalis was withdrawn on November 10, at which time she had had a total of 1.2 Gm. by mouth,

2 mg. of digoxin, and 9 cat units of digalen. This had caused green vision and partial blindness, as well as gastrointestinal disturbances. Two weeks after digitalis was withdrawn, the administration of only 3 grains of quinidine, on November 24, caused the cardiac mechanism to revert to normal sinus mechanism (Fig. 7, *F*). By this time the urinary abnormalities had disappeared and the blood pressure had fallen to 108/74. She was seen again in January, 1943, and at that time still had sinus rhythm.

CASE 8.—S. W., a colored man, aged 64 years, John Sealy Hospital No. 66680, entered the hospital Feb. 19, 1943, because of a syncopal attack which was followed by epigastric pain which radiated into the left shoulder. He had been under observation in the Out-patient Clinic and hospital since 1937 because of hypertensive heart disease. In January, 1943, he had been hospitalized for ten days after an attack of cerebral angiospasm. On Feb. 2, 1943, he visited the clinic, and the electrocardiogram taken at that time showed atrial fibrillation (Fig. 8, *A*). At the time of admission, on February 19, clinical signs suggested that fibrillation was still present. By the time a tracing was recorded, however, the ventricular rate was regular, and the cardiac mechanism was found to have changed to paroxysmal atrial tachycardia with A-V block, usually 2:1 (Fig. 8, *B*, *C*, and *D*). On February 20 the same mechanism was present at 10:00 A.M. (Fig. 8, *E*). At 11:00 A.M. the heart had again become irregular, and the tracing taken at noon showed atrial fibrillation or impure flutter (Fig. 8, *F*). On February 22, the tracing revealed atrial flutter with variable A-V block (Fig. 8, *G*). He was given 1.4 Gm. of quinidine, which produced sinus rhythm within seven hours (Fig. 8, *H*). Flutter reappeared on the morning of February 23, and 1.6 Gm. of quinidine were given; that afternoon atrial fibrillation or impure flutter was recorded (Fig. 8, *I*). On February 24, sinus rhythm had appeared, and this mechanism persisted until his discharge in April. He died suddenly May 11, 1943, during a convulsive seizure.

CASE 9.—A. H., a colored woman, aged 46 years, John Sealy Hospital No. 19506, was admitted to the hospital Jan. 15, 1942. She had congestive heart failure. The blood pressure, which had been known to be elevated since 1926, was 250/160 on admission. During the preceding four months, she had been on irregular doses of digitalis, but during the three weeks before admission there had been progressive edema and dyspnea. The heart was markedly enlarged, and severe failure was present. Ophthalmoscopic examination showed papilledema; nitrogen retention was present. The serum albumin was 3.44 per cent, and the globulin, 6.2 per cent. There was a rectal stricture caused by lymphopathia venereum.

The electrocardiogram on the day of admission showed atrial fibrillation (Fig. 9, *A*). The next day digitalis medication was begun in a dosage of 0.3 Gm. daily, and this was continued until her death. On January 16, the pulse rate was 134 per minute, and regular. On January 18, the heart was again irregular, and a tracing taken at this time showed paroxysmal atrial tachycardia with variable A-V block (Fig. 9, *B*). On January 20, 21, and 23, there was sinus rhythm at a rate of 133 to 136 per minute, recorded electrocardiographically (Fig. 9, *C*). On January 25 there were numerous paroxysms of tachycardia, during which there was again partial A-V block. Quinidine was given without improvement (Fig. 9, *D*).

Nitrogen retention had been progressive. Pericarditis was noted first on January 20. Death occurred from uremia on Jan. 26, 1942.

CASE 10.—C. O., a white man, aged 73 years, John Sealy Hospital No. 44749, was admitted April 17, 1942, with a right-sided hemiplegia; he was semicomatose and had Cheyne-Stokes respiration. Hypertension was present (180/104), the arteries were sclerotic, and the heart was large; congestive failure was present in moderate grade. On April 17 and 18 he was given 1 mg. of digoxin intravenously; on April 19 and 20 he received 0.5 mg.; aminophyllin, in doses of 0.5 Gm., was injected April 18, 19, and 20. Electrocardiograms taken April 18, and again on April 21, showed paroxysmal atrial tachycardia with 2:1 A-V
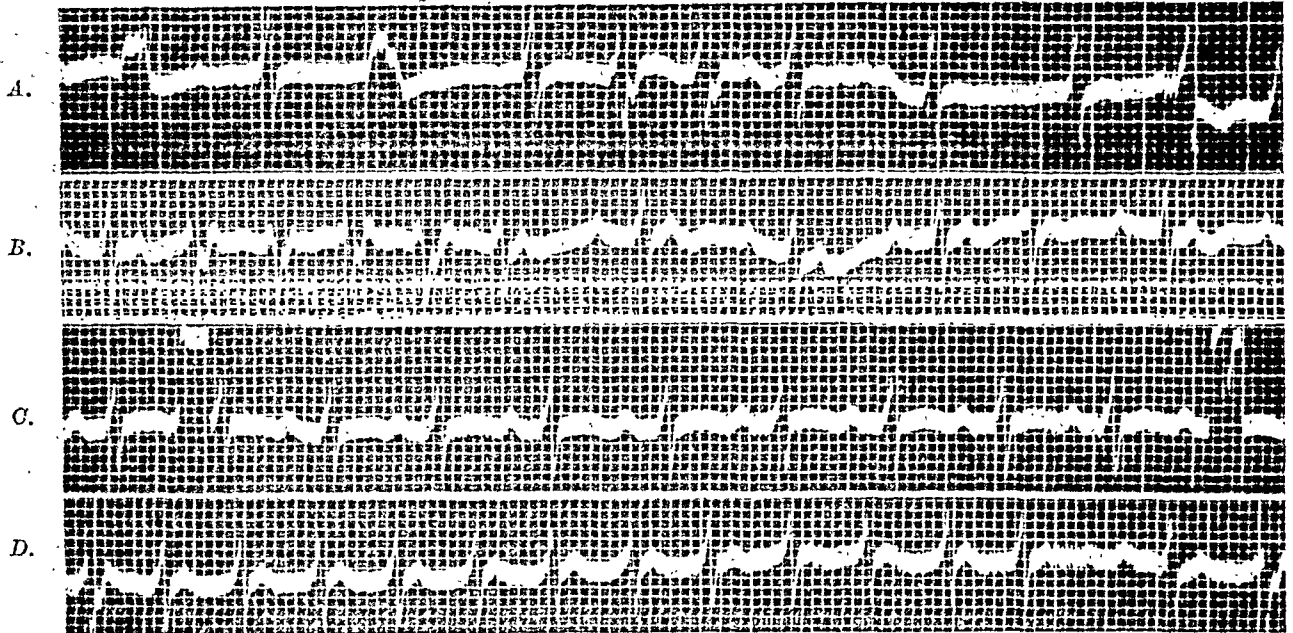
Fig. 9.—Case 9. *A*, Lead II, Jan. 15, 1942; atrial fibrillation. *B*, Lead II, January 18; atrial tachycardia with variable A-V block. *C*, Lead II; sinus rhythm on January 20. *D*, Lead II; recurrence of paroxysmal tachycardia on January 25.
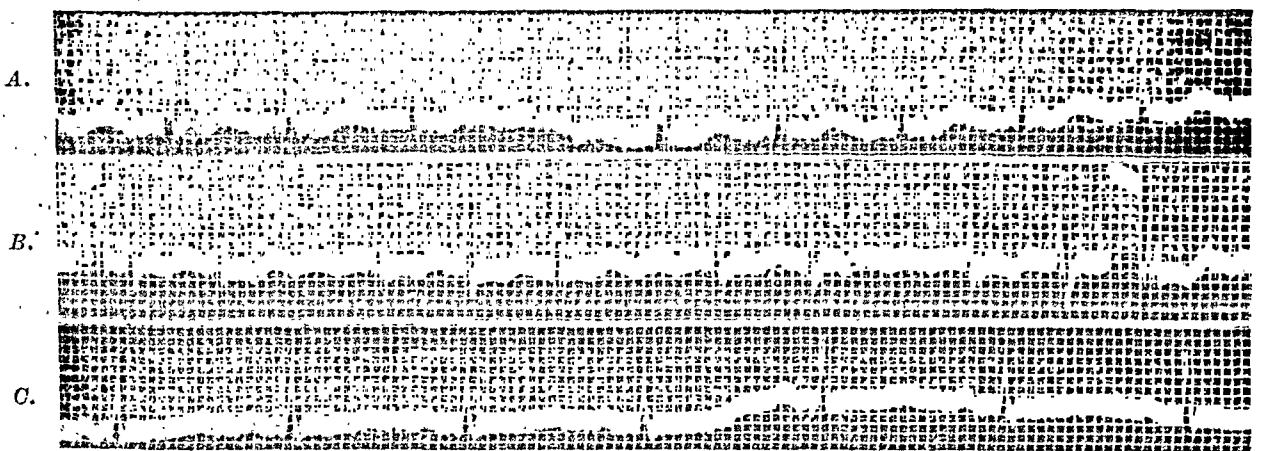
Fig. 10.—Case 10. *A*, Lead II, April 18, 1942; paroxysmal atrial tachycardia with 2:1 A-V block. *B*, Lead II, May 2; atrial flutter. *C*, Lead II; sinus rhythm on May 4.

block (Fig. 10, *A*). On April 24, frequent short paroxysms were noted clinically, although the electrocardiogram showed sinus rhythm with supraventricular premature beats. On May 2, the rhythm was irregular; the electrocardiogram revealed atrial flutter, with variable A-V block (Fig. 10, *B*); 0.6 Gm. of quinidine was given on May 3, which converted the mechanism to sinus rhythm (Fig. 10, *C*).

CASE 11.—J. S., a white man, aged 62 years, John Sealy Hospital No. 75448, was admitted July 20, 1942. He had Parkinson's disease, as well as hypertensive and arteriosclerotic heart disease, and had been hospitalized because of congestive heart failure in April, 1942. He stopped taking his maintenance dosage of digitalis about June 1, and resumed his occupation. Within two weeks, symptoms of failure reappeared, and these became progressively worse. At the time of admission the blood pressure was 160/120; the heart and liver were enlarged; edema of the lower extremities was marked. The venous pressure was 27 cm. of saline.
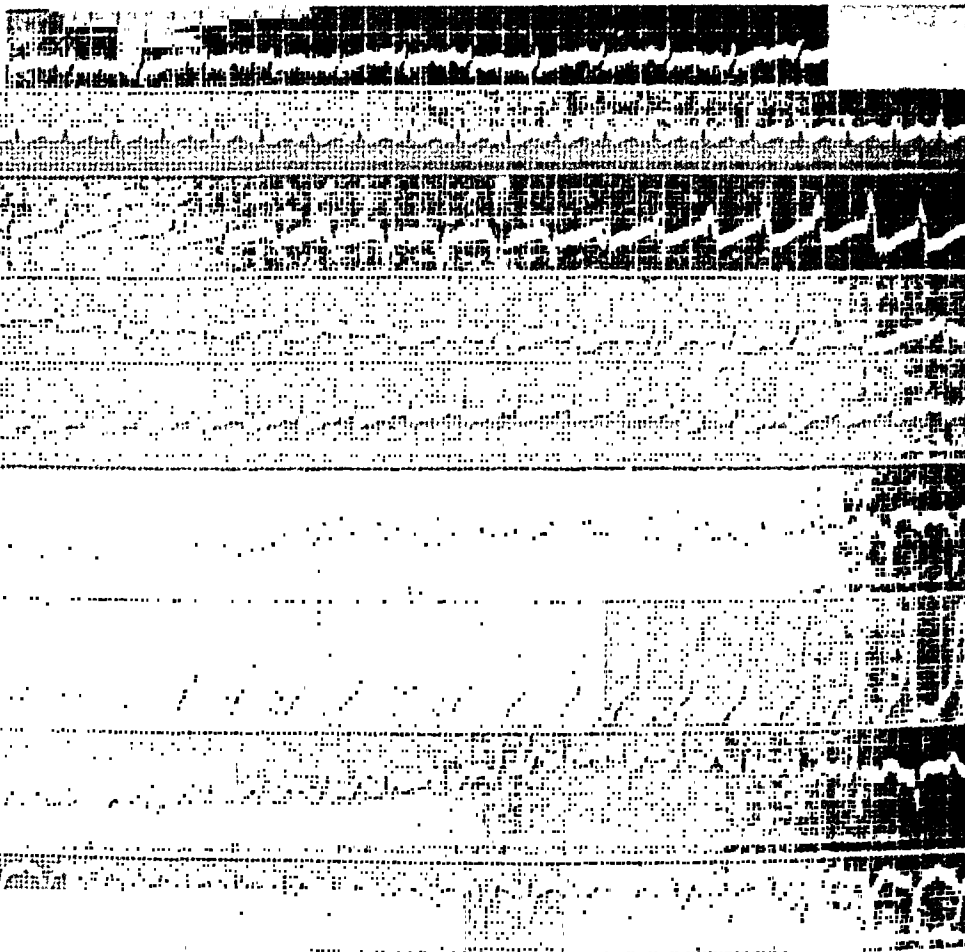
Fig. 11.—Case 11. A, Lead II, July 21, 1942: sinus rhythm. B, Lead II, July 23, 2:00 A.M.; paroxysmal atrial tachycardia. C, July 23, 1:17 P.M., Lead II; tachycardia with slower rate and much aberration of the QRS complexes. D, 2:50 P.M., Lead II; flutter with variable A-V block. E, 3:10 P.M., Lead II; flutter with 2:1 block. F, Lead CF₁, July 24; auricular tachycardia, with A-V block and independent ventricular rhythm. G, Lead II, July 25, morning; probably atrial tachycardia with QRS aberration. H, Lead II, July 25, afternoon; atrial tachycardia with variable rate, and probably complete A-V block. I, Lead II, July 27; showing the reappearance of flutter.

The cardiac rhythm was regular (Fig. 11, A), with atrial premature beats which were noted, clinically, to occur in frequent short runs. Pulmonary infarction with hemoptysis developed on July 21. Digitalis in a dose of 1.2 Gm. was given from July 20 to 23.

At 1:00 A.M. on July 23 he was found to have what was probably paroxysmal atrial tachycardia, with a rate of 170 per minute (Fig. 11,

B); carotid sinus pressure and the injection of 1 mg. of prostigmine were without effect; 5 mg. of neosynephrin were likewise ineffectual. At 1:00 P.M. of July 23, the rate had slowed to 150 per minute; there was marked, transient variation in the QRS complexes, with varying degrees of aberration (Fig. 11, C). At 2:50 P.M. atrial flutter was present with variable block (Fig. 11, D); 10 mg. of neosynephrin were given, and at 3:10 P.M. there was a regular 2:1 A-V block (Fig. 11, E); 2.1 Gm. of quinidine were given during the night, and the next day, July 24, the atrial rate had dropped to 240 per minute (Fig. 11, F); there was complete A-V dissociation, with an idioventricular rhythm at a rate of 122 per minute. On the morning of the 25th the heart rate was 150 per minute (Fig. 11, G); the mechanism may be ventricular tachycardia, but in view of the marked aberration of the QRS complex which had previously been present, we regard these as being of supraventricular origin, with defective bundle branch conduction; the P waves appear to be in the S-T segment. Two and four-tenths grams of quinidine were given in divided doses, and by late afternoon of July 25 the mechanism was again changed. The atrial rate varied from 210 to 250 per minute; the ventricular rate was 140, with probably complete A-V block (Fig. 11, H). This tracing is interpreted as representing a return to the atrial tachycardia that was previously present.

Prostigmine and quinidine were given repeatedly on July 26, but the heart rate remained between 140 and 150; 0.4 Gm. of digitalis produced no change in rate. The tracing taken on July 27 shows a ventricular rate of 167 per minute; atrial flutter is present at a rate of 300 per minute (Fig. 11, I). Death occurred July 28.

Necropsy showed a heart weighing 470 grams. Coronary arteriosclerosis was present, and, although no coronary thrombosis was found, there was a myocardial infarct at the tip of the left ventricle. Mural thrombi were present in the left ventricle adjacent to the myocardial infarct, and also in the right atrium. There were embolic infarcts of the lungs, and of the kidneys, spleen, and brain.
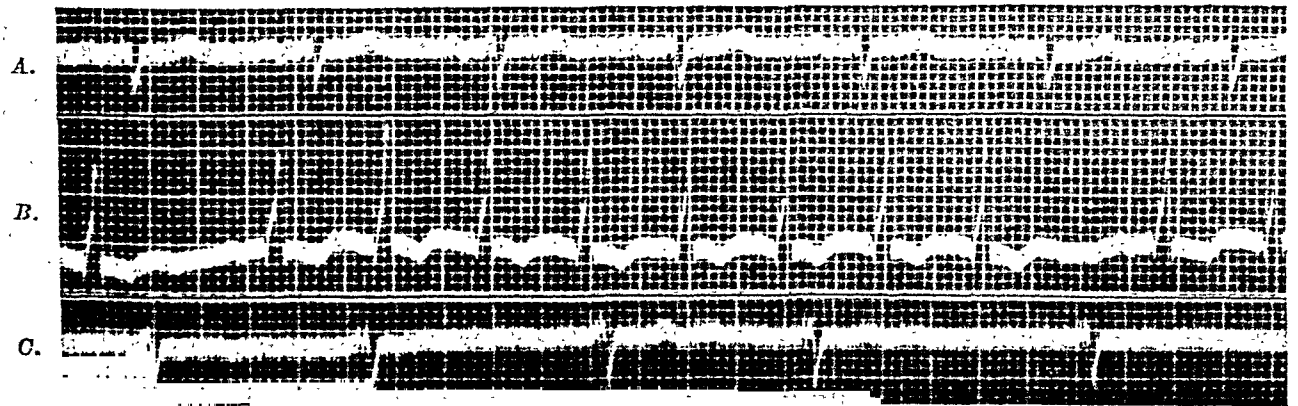
Fig. 12.—Case 12. A, Lead II, Aug. 28, 1942; sinus rhythm. B, Lead IVF, August 30; showing a short paroxysm of tachycardia. C, Lead II, September 1; atrial fibrillation.

CASE 12.—M. G., a white man, aged 46 years, John Sealy Hospital No. 77524, entered the hospital Aug. 27, 1942, with congestive heart failure of four months' duration due to arteriosclerotic heart disease. Digitalis medication was as follows: August 29, 0.6 Gm., August 30, 31, and September 1, 0.4 Gm.; beginning September 2, 0.1 Gm. daily. On August 28, the electrocardiogram showed sinus rhythm at a rate of

79 per minute (Fig. 12, *A*); the situation was the same on August 29. The tracing taken August 30 (Fig. 12, *B*) showed frequent short paroxysms of supraventricular tachycardia, at a rate of 150 per minute,
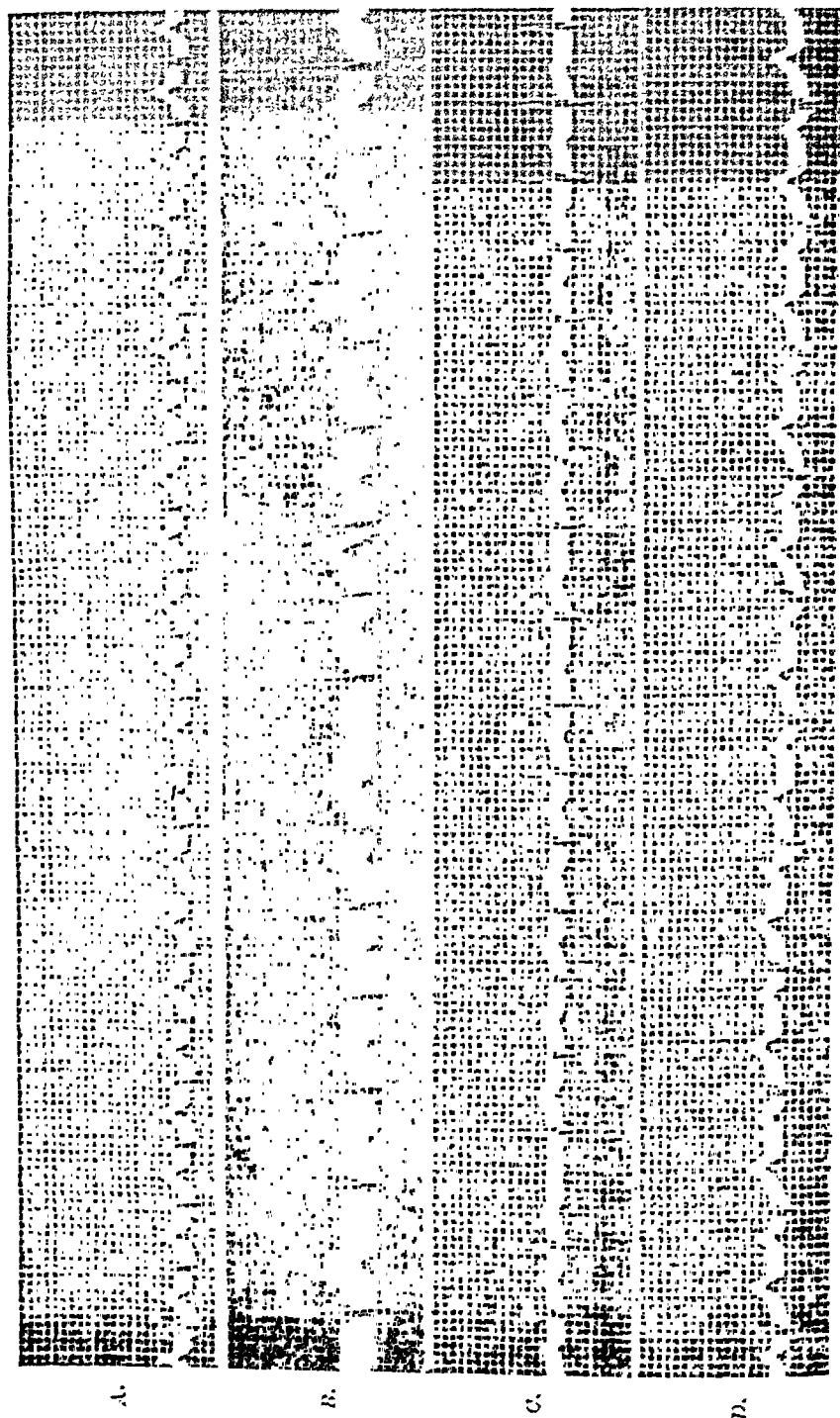
Fig. 13.—Case 13. *A*, Lead II, Nov. 17, 1912; paroxysmal atrial tachycardia. *B*, Lead II, June 10, 1913; atrial fibrillation, immediately after the spontaneous termination of a typical paroxysm of tachycardia. *C*, Lead II, June 10; three hours after *B*, Lead II, June 10; sinus rhythm; one hour after 3 grains of quinidine.

in some of which there was partial A-V block. The curves taken the next day, August 31, disclosed that the mechanism had changed to atrial fibrillation (Fig. 12, *C*). The fibrillation persisted until October 21; on this day sinus rhythm reappeared, and persisted.

CASE 13.—J. H., a white man, aged 48 years, John Sealy Hospital O.C. No. 112683, attended the clinic for antisyphilitic treatment. He had had a penile chancre, in 1916, which had been treated locally with calomel. A recent blood Wassermann reaction had been found to be positive. When he was examined on Nov. 11, 1943, his heart was considered normal; the blood pressure was 136/86. However, he gave a history of having had paroxysms of tachycardia for the preceding twenty-five years. These varied in frequency as well as duration; they lasted from ten minutes to several hours, and often stopped spontaneously. On other occasions the paroxysms could be terminated by bending, straining, or gagging. While visiting the clinic on November 17 he had a typical paroxysm. Electrocardiograms were obtained, and showed paroxysmal supraventricular tachycardia at a rate of 231 per minute (Fig. 13, A). Carotid sinus pressure was without effect. Prostigmin in a dose of 1 mg. was injected, and fourteen minutes later the paroxysm was terminated. After the paroxysm, the electrocardiogram showed no abnormalities.

Between November, 1942, and June, 1943, he was given twenty injections of bismuth and four injections of an arsenical. On June 10, he was again seen in the clinic in a typical attack of paroxysmal tachycardia. The rate was 250 per minute, and the rhythm was regular. Before the electrodes could be applied the patient volunteered the information that the attack had ceased spontaneously. When his pulse was felt it was found to be much slower, but irregular. The electrocardiogram taken at this time, 11:30 A.M., showed atrial fibrillation, with a ventricular rate of about 160 per minute (Fig. 13, B). He was observed for three hours in anticipation of spontaneous reversion of the fibrillation; at 2:30 P.M. fibrillation was still present (Fig. 13, C). A test dose of 3 grains of quinidine was given; an hour later normal sinus rhythm was present (Fig. 13, D).

CASE 14.—P. J., a colored man, aged 76, John Sealy Hospital No. 78053, was admitted March 1, 1943, because of congestive heart failure which had gradually become manifest during the preceding two years. For the preceding eighteen days dyspnea and edema had become severe. The blood pressure was 200/90; the heart was enlarged, and there were the usual evidences of heart failure of moderate grade. The venous pressure was 21.5 cm. of saline. The electrocardiogram on March 2 showed sinus rhythm with frequent ventricular premature beats. Digitalis was begun on March 2, and, by March 5, 1.2 Gm. had been given; after this day, 0.1 Gm. was given daily. By March 5 atrial fibrillation was present, and was recorded on March 9 and again on March 16 (Fig. 14, A). Quinidine was administered in a dose of 0.6 Gm. daily from March 3 to 17; on March 18, 2 Gm. were given; from March 19 to 26 the 0.6 Gm. dosage was resumed.

On March 20 the electrocardiogram showed paroxysmal atrial tachycardia with an atrial rate of 166 to 171 per minute, and with 2:1 and 3:2 A-V block. The tachycardia was still present on March 22, with 2:1 A-V block at an atrial rate of 214 per minute; an hour later the atrial rate had dropped to 162, and 1:1 conduction occurred; at this time 1 mg. of prostigmin was given, and, although the atrial rate was only 171 to 179 per minute, A-V block appeared, varying from 3:2 to 2:1 (Fig. 14, B).

The tracing taken March 23 is of particular interest, and all of Lead II is reproduced (Fig. 14, C and D). The atrial rate varies from 260
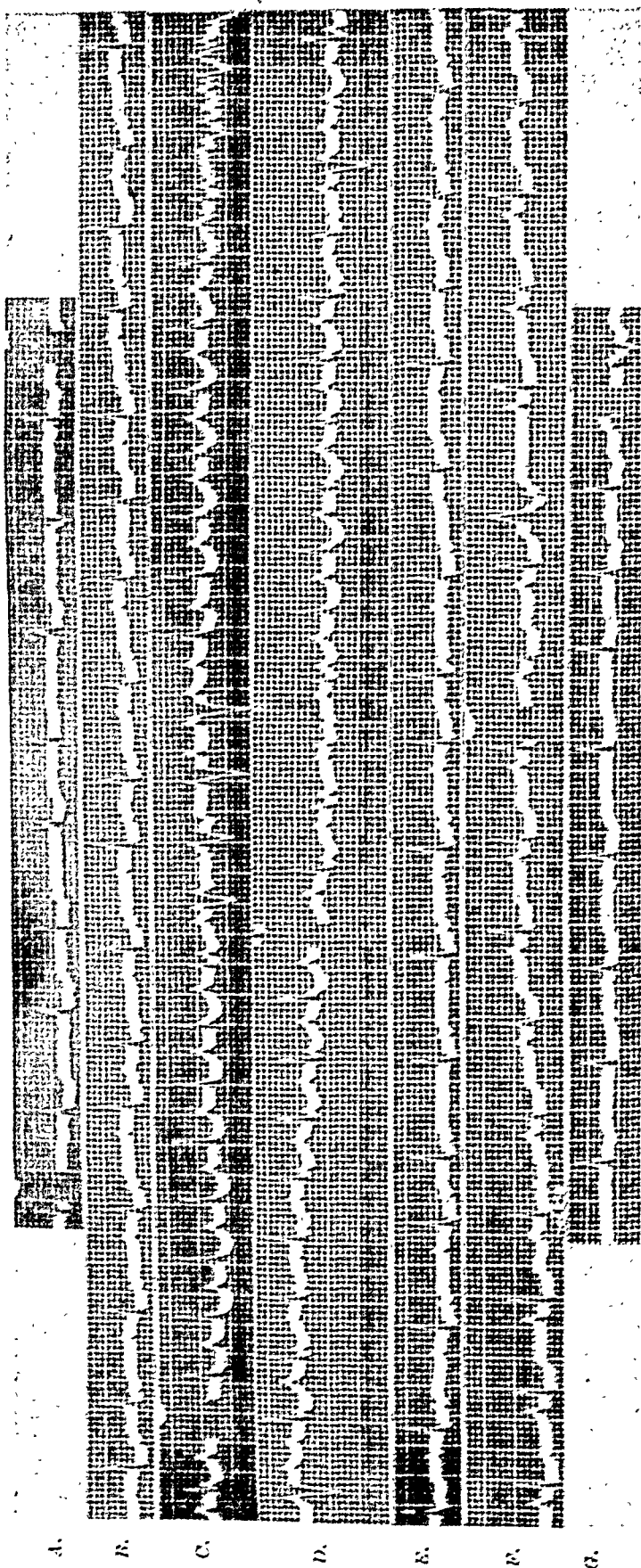
Fig. 11.—Case 11. A, Lead II, March 8, 1943; atrial fibrillation. B, Lead II, March 22; showing tachycardia with A-V block. C and D, Continuous strips of Lead II, March 23; showing variation in atrial rate, and possibly cyclic variation between tachycardia and flutter. E, Lead II, March 25; tachycardia with A-V block. F, Lead II, March 29. G, Lead II; sinus rhythm on March 29. F, Lead II; atrial fibrillation again on May 11, 1943.

to 316; at the slower rates the tracing seems definitely to be atrial tachycardia; at the more rapid rates the presence of flutter seems equally certain. Although it is difficult to be positive, the curve is very suggestive of cyclic variation between atrial tachycardia and atrial flutter. The tracings taken on March 25 and 26 showed tachycardia with partial A-V block, usually 2:1 (Fig. 14, E). On March 29th, sinus rhythm was present (Fig. 14, F). The patient was discharged April 4, 1943, on a maintenance dose of digitalis.

He returned to the Out-patient Clinic on April 27 with extreme cardiac failure. The electrocardiogram showed a return of atrial fibrillation. Diuresis was obtained with ammonium chloride and mercupurin, with clinical improvement. On May 4, the mechanism had changed to sinus rhythm. On May 11, however, the digitalis was discontinued because of nausea and vomiting; on this day the tracing showed atrial fibrillation (Fig. 14, G). He was not seen again until June 3, at which time the severity of his cardiac failure necessitated hospitalization. The last electrocardiogram showed sinus rhythm. He died June 4, 1943.

<div align="center">COMMENT</div>

The intimate relationship of atrial flutter and fibrillation is well recognized. The older theories of the mechanism of these disturbances have been reviewed by Garrey,[11] who also summarized the available evidence in favor of the theory of a circus mechanism. This latter concept has found wide acceptance, although the Viennese group of cardiologists prefer the concept of one or more rapidly discharging ectopic or parasystolic foci operating to produce either flutter or fibrillation. The circus mechanism may be modified by assuming a single initial premature stimulus, followed by multiple re-entries. Lack of conclusive evidence for any one of these possible mechanisms does not vitiate the fact that the same fundamental mechanism appears to be operative for both flutter and fibrillation. This is amply substantiated by both laboratory and clinical experience.

Paroxysmal atrial tachycardia, however, has been generally thought to be the result of a totally different mechanism. The most widely held view is that paroxysms result from the rapid discharge of impulses from an ectopic pacemaker. Multiple re-entries from a single impulse, and the removal of blocking from a parasystolic focus have also been proposed. The views concerning the possible mechanism of paroxysmal ventricular tachycardia, many of which are equally applicable to the atrial variety, have recently been reviewed by Cooke and White.[12]

Suggestions have not been entirely lacking that paroxysmal tachycardia is due to a mechanism similar to that responsible for flutter and fibrillation. Iliescu and Sebastiani[13] noted the similarity between the action of quinidine in cases of paroxysmal tachycardia and its effect in flutter and fibrillation. They stated that quinidine produces a marked slowing of the atrial rate in fibrillation, less in flutter, and still less in tachycardia, and considered that the variation in its action was quantitative rather than qualitative, and might depend in part on the original

atrial rate. The preliminary slowing of the atrial rate, and subsequent abrupt transition to normal mechanism, suggested to them the possibility that paroxysmal tachycardia, as well as flutter and fibrillation, might be the result of a circus mechanism.

Ashman and Hull[14] have given as their view the concept that paroxysmal tachycardia is due in many instances to a circus mechanism which passes through the S-A or A-V node. If this were so, the susceptibility of the tachycardia to termination by reflex vagal stimulation would result from vagal influence on the nodal portion of the circuit. Presumably, also, the isoelectric period of the electrocardiogram, the chief criterion for differentiation from flutter, would coincide with the relatively slow passage of the impulse through the nodal tissue.

More recently, Barker, et al.,[15] have discussed the similarity, as well as the differences, between tachycardia and flutter-fibrillation. They believe that paroxysmal tachycardia, particularly in those cases in which there is either A-V block or alternation of the P-P cycle length, may best be explained by assuming that a circus mechanism passes through the S-A or A-V node. The experimental reproduction by Butterworth and Poindexter,[16] of the Wolff-Parkinson-White syndrome of short P-R interval with prolonged QRS complex indicates strongly that there is a circus movement during the paroxysms of tachycardia which are typically associated with this syndrome. Presumably the circus moves down the A-V conduction tissue, and re-enters the atrium through the bundle of Kent.

We do not believe that our own data can be used as evidence in favor of any one of the hypotheses for the fundamental mechanism of these disturbances. However, the fact seems clearly established that some cases of paroxysmal atrial tachycardia are closely related to flutter and/or fibrillation.

This is particularly true of those cases of tachycardia in which partial A-V block has been found to exist at some time, thus confirming the same observation by Barker and his associates.

Whether this is a coincidence, or actually indicates a circus mechanism in these cases of paroxysmal tachycardia, must be ascertained by more definitive means. As an initial effort in this direction, we have recently calculated the electrical axes of the P waves at $\frac{1}{100}$ second intervals, using simultaneous chest leads placed in three planes, as was done by Lewis, et al.[17] Judging from our experience to date,[18] we believe that the method is capable of showing the existence of a circus movement, if one be present. At least, our results in flutter and fibrillation seem to agree in general with those obtained by Lewis. However, in four cases of paroxysmal atrial tachycardia with A-V block, the curves representing the consecutive electrical axes of the atrium fail to suggest a circus movement; they rather resemble the curves obtained from individuals with normal sinus rhythm, differing only in their direction. These data will be reported soon in detail.

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MEASUREMENTS OF ARTERIAL BLOOD PRESSURE IN THE ARM AND LEG: COMPARISON OF SPHYGMOMANOMETRIC AND DIRECT INTRA-ARTERIAL PRESSURES, WITH SPECIAL ATTENTION TO THEIR RELATIONSHIP IN AORTIC REGURGITATION

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THE commonly used clinical methods of measuring arterial blood pressure are based on the concepts proposed originally by Riva-Rocci,[1] von Recklinghausen,[2] and Korotkow.[3] Examination of the original articles of these writers reveals that their technique is founded on indirect evidence. Many attempts have been made to study the accuracy of clinical methods of measuring blood pressure, but, prior to 1931, these could be based only on theoretical deductions. In that year, Wolf and von Bonsdorff[4] introduced a method for accurate optical recording of human blood pressure by arterial puncture, thereby permitting direct observation of the accuracy of bloodless methods.

The various factors influencing the measurement of blood pressure in the brachial artery by the cuff method have been studied in adults[5] and children[6] by Hamilton and his co-workers, and more recently in adults by Ragan and Bordley.[7] These workers have found that the standard arm cuff (12 to 13 cm. wide) does not permit accurate measurement of blood pressure in all subjects, and that no definite method of prediction permitted choice of a cuff of proper width, either for children or some adults.

Although Hales,[8] in 1733, employed the femoral artery of a horse in the first recorded direct measurement of blood pressure, and although many investigators have used it in animal experiments since, there have been relatively few studies of femoral blood pressure in man by direct methods. Thus, the accuracy of clinical methods of measurement of femoral blood pressure cannot be regarded as established. In 1939, The American Heart Association and the Cardiac Society of Great Britain and Ireland[9] recommended a cuff 15 cm. wide for use on the thigh. The exact reasons for this choice were not given, although Recklinghausen[2] had stated that a cuff of 15 cm. was wide enough for any extremity. However, there is no experimental verification that this or any other cuff is adequate for accurate measurements of femoral blood pressure.

There is little agreement regarding the relation of femoral and brachial blood pressure. The usual clinical concept is that the femoral systolic blood pressure is approximately equal to the brachial systolic blood pressure in normal persons, but that in aortic insuf-ficiency and under certain other conditions it is considerably higher. Hamilton and his co-workers[5] demonstrated by arterial puncture that the femoral systolic blood pressure is higher than the brachial in normal persons, although he did not specify the number of subjects studied. The femoral diastolic pressure was found to be the same or slightly lower than the brachial diastolic pressure. Wolf and Bons-dorff,[4] on the other hand, compared the femoral pressure, as ascer-tained by arterial puncture, with the arm pressure, as ascertained by the usual Korotkow method, in six subjects without valvular dis-ease or hypertension. In an analysis of this material, they concluded that "there could be no great difference between the femoral and brachial pressure" in man.

In the present study, blood pressure was measured in the brachial and femoral arteries of subjects with normal pressures, hypertension, and aortic insufficiency by cuff methods and by use of the optical manometer. We desired, first, to test the accuracy of the 15 cm. cuff for measurements of blood pressure in the thigh; second, to test the validity of the impression that aortic regurgitation produces a disproportionate elevation of the systolic pressure in the leg (thigh); and, third, to compare the respective femoral pressures with the con-comitant pressures in the arm.

<div align="center">METHOD</div>

Direct measurements of femoral and brachial blood pressure were made on cooperative, convalescent subjects from the hospital wards. Repeated measurements with the cuff were made on the extremity in question until the blood pressure range was stable, before, during, and after the optical manometric measurements. Systolic levels were read at the first appearance of sound, and diastolic levels at the point at which sounds become dull and muffled (between third and fourth phases). For the arm the standard 13 cm. cuff was used; for the leg we employed both the standard arm cuff (called the "narrow leg cuff" in this report), as well as a specially made cuff, 15½ cm. wide, tapered 4 cm. at this lower edge for better fit. The cloth covering of the wider leg cuff was 2 cm. wider and 2 cm. longer than the rubber bag, and the cuff wrapper measured 130 cm. in length. this varies but slightly from the specifications proposed for the leg cuff by The American Heart Association and the Cardiac Society of Great Britain and Ireland.

Direct intra-arterial measurements were made with the Hamilton manometer as modified by Gregg, et al.[10] The membranes used were usually rubber* (cardiovascular sheeting, 0.028 inch thick), although glass spoons† were used in a few experiments. Neither possessed

greater advantage in our hands. The frequency of these membranes, as tested before each experiment, was at least 80 double vibrations per second; Frank[11] considered 40 double vibrations per second adequate for recording most of the peripheral pulse wave characteristics.

The light source was a 500 watt Mazda projection light, placed 12 cm. behind an adjustable vertical slit, and directed upon a small plane mirror mounted on the membrane which the arterial pulsations moved. The image was focused by a convex lens of low power upon the revolving paper film of the Cambridge research model electrocardiograph, 140 cm. distant. The apparatus was adjusted so that the level of the artery to be punctured was on the same plane as the fluid levels in two pressure reservoirs, one of which contained 5 per cent sodium citrate solution, and the other, water; readings were thus corrected automatically for the level of the puncture site.

For the procedure itself a cooperative patient was placed supine on a flat table and the extremity to be studied was placed comfortably in a natural position. The puncture site in the brachial artery was the antecubital fossa, just above the anterior crease of the elbow, and, in the femoral artery, the femoral triangle just below the inguinal ligament. Before puncture, these areas were cleansed with iodine and alcohol, and the skin and subcutaneous tissue, down to the artery, were infiltrated with 1 per cent procaine solution. The only pain which the subjects noted was felt as a brief twinge at the moment of arterial puncture.

After blood pressures were taken with the proper cuff and found stable, the artery was punctured, using a sterile, short bevelled, No. 21 needle, 1⅝ inches in length over all. The needle was inserted into the artery with the bevel close to the perpendicular. After graphic registration of the blood pressure, the cuff measurements were repeated; in the case of the arm, checks were made at some point while the manometer was recording.

Graphic records were taken at two speeds; pressure and time measurements were made from the higher speeds for greater accuracy. The membrane was then calibrated in millimeters of mercury with the needle in place, using a mercury-filled U tube and the pressure bottle; calibrations were made every 50 mm. Hg up to a pressure of 250 mm. Hg. After calibration, another graphic record was usually made, unless the citrate in the tubing was inadequate to prevent clotting during this period. It is worth noting that none of the citrate entered the circulation or surrounding tissue. After removing the needle, firm compression was applied to the artery for five minutes.

If, as infrequently happened, the artery could not be readily entered, the experiment was immediately abandoned, rather than risk injury to the vessel or excitement to the patient.

Simultaneous registration of the femoral and brachial blood pressures was not done, but they were measured in quick succession (about 5 to 8 minutes apart) without apparent change in the patient's mental or physical state. In about half the experiments, the arm pressures were measured first, and in the remaining group, the leg measurements were made first.

RESULTS

Measurements were done on nine patients with normal blood pressure, nine patients with hypertensive cardiovascular disease, and ten

patients with aortic insufficiency. The results are listed in Table I. In all instances in which there was a range in cuff pressures* after the initial fluctuations had disappeared, a range is listed. All subjects, except one, showed some variation (mainly respiratory) in the height of the manometric recordings; this was pronounced in some and slight in others, but always more marked in the systolic level. For purposes of comparison, average cuff pressures were compared with average manometric pressure. Differences of less than 10 mm. of mercury were considered within the limits of error of the graphic method, because of experimental conditions.

Reference to Table II will show the differences between direct pressures in the brachial and femoral arteries and the percentage error from use of the respective cuffs on the arm and thigh. In this table and the following discussion the values obtained by direct methods are considered to represent the true intra-arterial pressure; and the results from use of the cuff are taken to be the values which may deviate one way or the other from the true direct pressure. Cuff and direct readings on the normal subjects show a fair agreement in the brachial systolic pressures, except in two subjects. The brachial diastolic cuff pressures were usually disproportionately higher; others[5, 7] have noted the character and direction of this disagreement. In the subjects with normal blood pressures, both the narrow and the wide leg cuffs gave results which were usually too high for the systolic, and always considerably higher for the diastolic pressures, when these values were compared with manometric readings.

Cuff measurements and direct brachial recordings on the subjects with hypertension showed a fair agreement of the systolic pressures in all but two patients, in both of whom the cuff pressures were too low (minus 27 and minus 20 mm. mercury). The brachial diastolic cuff pressures were too high in five of the nine subjects in this group. Again, the narrow cuff gave readings of the femoral blood pressures which were consistently too high for both the systolic and diastolic levels. The wide cuff permitted a somewhat better estimation of the femoral systolic pressure in those patients on whom it was used; the diastolic readings with the wide cuff were uniformly too high, averaging 14 mm. above graphic pressure.

Cuff and graphic arm readings on the patients with aortic insufficiency showed a fair agreement in the systolic level. The brachial diastolic pressures agreed in only one subject (Case 2). In two patients with aortic regurgitation (Cases 6 and 9), whose sharp arterial sounds were heard down to zero pressure in both arm and leg, the true brachial diastolic pressure was found to be 41 mm. and 35 mm. Hg, respectively. Femoral wide cuff pressures were consistently too

*In the following discussion the words "direct," "manometric," and "graphic" refer to arterial blood pressures obtained by use of the optical manometer; "cuff" pressure refers to that obtained by use of the arm or leg cuffs, mercury manometer, and the auscultatory technique.

TABLE I

CASE NUMBER	NAME	DIAGNOSIS	BRACHIAL				FEMORAL				
			CUFF PRESSURE	GRAPHIC RANGE	GRAPHIC AVERAGE	PULSE RATE AVERAGE	WIDE CUFF PRESSURE	NARROW CUFF PRESSURE	GRAPHIC RANGE	GRAPHIC AVERAGE	PULSE RATE AVERAGE
						Control Group					
1	M. H.	Convalescent pneumonia	115/70	122-116/63-58	119/61	56	135/90	150/90	130-128/59-55	129/57	58
2	A. R.	Syphilitic cerebral thrombosis	106/84-78	107-105/67-63	106/65	77	120/78	155/105	105-99/59-55	102/57	77
3	J. M.	Peptic ulcer (post bleeding)	126-105/65-56	94-92/47	93/47	74		124/80	105-93/34	99/34	70
4	C. Z.	Convalescent pneumonitis	118-105/66-60	124-110/63-57	117/60	75	132-130/74-70	132/78	139-123/63-53	131/58	81
5	G. C.	Cholangitis	110/75-70	117-110/66-62	113/64	55	120/90	130/100-95	133-118/70	125/70	56
6	C. P.	Rheumatic fever	125-120/75-70	129-119/71-66	124/69	86	135-130/95-90	145-140/95-90	138-129/68-61	134/65	80
7	R. M.	Rheumatic fever	120/70	138-130/77-74	134/76	96	135-130/80-75	155/105	130-124/65	127/65	96
8	Z. M.	Convalescent pneumonia	140-135/85	133-130/90-84	132/87	110	155-150/95-90	165/105	159-148/86-77	154/82	112
9	W. J.	Uncontrolled diabetes	135-130/90-85	136-132/83-78	134/81	80	135-130/95	165-160/110-105	140-125/80-73	133/77	77
						Hypertensive Patients					
1	P. A.	Hypertensive heart disease (mild failure)	188-170/105-100	215-203/95-88	209/92	55	238-235/110-108	270/130	224-215/81-74	219/78	57
2	C. H.	Hypertension	210-205/140	214-206/129-119	210/124	86		260/160	222-214/131-123	218/128	92
3	W. J.	Hypertension hemiplegia	200/155	198/126	198/126	89		260/180	215-211/123	213/123	86
4	S. W.	Hypertension	195-190/108	215-190/112-107	196/110	96		240/140	220-196/109-89	208/99	96

No.	Pt.	Diagnosis									
5	M. M.	Rheumatoid arthritis	180-168/82-78	183-158/85-75	171/80	83	170-165/85		176-162/71-62	169/67	80
6	W. H.	Hypertension hemiplegia	173-165/120-115	192-185/115-108	189/112	97	195-180/135-120		200-187/114-111	193/113	90
7	M. R.	Hypertensive encephalopathy	155-146/108-98	143-131/94-87	137/91	84	185-160/120-100		143-130/91-82	137/87	79
8	J. A.	Diabetes	190-180/120-115	204-188/115-103	196/109	98	205-200/120	245/160	197-175/115-106	186/111	96
9	J. R.	Carcinoma of stomach	165-155/90-85	164-148/82-76	156/79	94	180/100	210-200/125	171-163/87-79	167/83	93

Patients With Aortic Insufficiency

No.	Pt.	Diagnosis									
1	M. C.	Syphilitic aortic regurgitation	140-135/35-30	135-128/21-16	132/19	82	215/30	250-235/50-35	161-149/17-7	155/12	81
2	J. B.	Syphilitic aortic regurgitation	160-145/50-45	155-124/57-33	140/45	74	240/55	295-275/60-55	183-146/43-24	165/34	79
3	G. N.	Syphilitic aortic regurgitation	145/55	148-142/40-35	145/38	90		210-205/80-70	152-142/35-30	147/33	92
4	R. G.	Syphilitic aortic regurgitation	170/85	187-178/72-66	183/69	66		200/105	207-197/81-71	202/76	75
5	A. C.	Aortic regurgitation	170-160/68-60	172-163/52-47	168/50	84		175/70	161-150/45-41	156/43	84
6	S. M.	Rheumatic aortic regurgitation	134/0	139-130/43-39	134/41	72	200/0	210/0	150-140/46-39	145/43	70
7	G. M.	Acute aortic endocarditis	112/44	104-100/41-38	102/39	77	145/55		116-107/36-34	112/35	78
8	W. G.	Syphilitic aortic regurgitation hypertension	160-155/105	149-142/93-90	146/92	85	188/118	210/125	176-159/92-81	168/87	82
9	T. G.	Syphilitic aortic regurgitation	145-136/0-0	137-124/40-30	131/35	90	230/0	240/0	200-178/37-34	189/36	89
10	M. W.	Syphilitic aortic regurgitation	165-155/60	175-170/45-41	173/43	86	195-185/50-45	215-205/55-50	160/37	160/37	84

TABLE II

CASE NO.	NAME	DIAGNOSIS	DIRECT LEG/ARM DIFFERENCE (SYSTOLIC/DIASTOLIC) (MM. HG.)	BRACHIAL ARM CUFF ERROR (SYSTOLIC/DIASTOLIC) (%)	FEMORAL WIDE (15.5 CM.) CUFF ERROR (SYSTOLIC/DIASTOLIC) (%)	FEMORAL NARROW (12 CM.) CUFF ERROR (SYSTOLIC/DIASTOLIC) (%)
		Control Group				
1	M. H.	Convalescent pneumonitis	+10 / −4	−3 / +14	+4 / +58	+16 / +58
2	A. R.	Syphilitic cerebral thrombosis	−4 / −8	0 / +24	+17 / +37	+52 / +84
3	J. M.	Peptic ulcer	+6 / −13	+24 / +29		+25 / +135
4	C. Z.	Convalescent pneumonitis	+14 / −2	−4 / +5	0 / +26	0 / +34
5	G. C.	Cholangitis	+12 / +6	−2 / +14	−4 / +22	+4 / +40
6	C. P.	Rheumatic fever	+10 / −4	0 / +5	0 / +30	+7 / +43
7	R. M.	Rheumatic fever	−7 / −9	−10 / −8	+4 / +20	+22 / +62
8	Z. M.	Convalescent pneumonitis	+22 / −5	+4 / −2	0 / +11	+7 / +28
9	W. J.	Uncontrolled diabetes	−1 / −4	0 / +7	0 / +19	+23 / +40
	AVERAGE CUFF ERROR (SYSTOLIC/DIASTOLIC) (%)			+1.0 / +9.7	+2.6 / +28	+17 / +58
		Hypertensive Patients				
1	P. A.	Hypertensive heart disease (mild failure)	+10 / −14	−17 / +12	+9 / +40	+23 / +66
2	C. H.	Hypertension	+8 / +4	0 / +13		+19 / +25
3	W. J.	Hypertension hemiplegia	+15 / −3	0 / +23		+22 / +46
4	S. W.	Hypertension	+12 / −11	0 / 0		+15 / +41
5	M. M.	Rheumatoid arthritis	−2 / −13	0 / 0	0 / +27	
6	W. H.	Hypertension hemiplegia	+4 / +1	−11 / +5	−3 / +13	
7	M. R.	Hypertensive encephalopathy	0 / −4	+10 / +13	+26 / +26	+78 / +84
8	J. A.	Diabetes	−10 / +2	−6 / +8	+9 / +8	+10 / +13
9	J. R.	Carcinoma of stomach	+11 / +4	+3 / +11	+8 / +21	
	AVERAGE CUFF ERROR (SYSTOLIC/DIASTOLIC) (%)			−2 / +9	+8 / +23	+28 / +46

TABLE II—CONT'D

CASE NO.	NAME	DIAGNOSIS	DIRECT LEG/ARM DIFFERENCE (SYSTOLIC/DIASTOLIC) (MM. HG.)	BRACHIAL ARM CUFF ERROR (SYSTOLIC/DIASTOLIC) (%)	FEMORAL WIDE (15.5 CM.) CUFF ERROR (SYSTOLIC/DIASTOLIC) (%)	FEMORAL NARROW (12 CM.) CUFF ERROR (SYSTOLIC/DIASTOLIC) (%)
		Patients With Aortic Insufficiency				
1	M. C.	Syphilitic aortic regurgitation	+23 / −7	+ 5 / +74	+39 / +150	+54 / +258
2	J. B.	Syphilitic aortic regurgitation	+25 / −11	+ 9 / + 7	+45 / +62	+73 / +71
3	G. N.	Syphilitic aortic regurgitation	+ 2 / − 5	0 / +45		+41 / +127
4	R. G.	Syphilitic aortic regurgitation	+19 / + 7	− 7 / +23		0 / +38
5	A. C.	Syphilitic aortic regurgitation	−12 / − 7	− 2 / +28		+12 / +63
6	S. M.	Rheumatic aortic regurgitation	+11 / + 2	0 / −	+38 / −	+45 / −
7	G. M.	Acute aortic endocarditis	+10 / − 3	+10 / +13	+29 / +57	
8	W. G.	Syphilitic aortic regurgitation hypertension	+22 / − 5	+ 8 / +14	+12 / +36	+25 / +44
9	T. G.	Syphilitic aortic regurgitation	+58 / + 1	+ 8 / −	+22 / −	+27 / −
10	M. W.	Syphilitic aortic regurgitation	−13 / − 6	− 8 / +40	+19 / +30	+31 / +43
AVERAGE CUFF ERROR (SYSTOLIC/DIASTOLIC) (%)				+ 2.3 / +24	+29 / +67	+34 / +92

high, especially for the systolic, but also for the diastolic, level. These differences were greatly exaggerated by the use of the narrow cuff. The femoral diastolic pressures in the same two subjects whose cuff readings on arm and leg were zero were 43 and 36 mm. Hg, respectively. The femoral pressure with the wide or narrow cuff approached accuracy in only one systolic reading and in no diastolic readings in the patients with aortic regurgitation.

Comparison of the graphic blood pressures in the arm and leg showed a noteworthy elevation of systolic pressure (+10 mm. Hg, or more) in the femoral artery in five of the nine control subjects. In the hypertensive group a noteworthy elevation of the femoral over the brachial systolic graphic pressures was noted in four of the nine patients; one subject presented a lower systolic pressure (−10 mm.) in the leg than in the arm. In aortic regurgitation the graphic systolic pressure was significantly higher in the leg in seven of the ten cases studied; in two patients the graphic systolic pressure was lower in the leg than in the arm. The graphic diastolic pressures in the arm and leg showed less consistent differences. However, the femoral

diastolic pressure was definitely lower in the leg than in the arm in one control subject (−13 mm. Hg), in three hypertensive subjects (−14, −11, and −13 mm. Hg), and in one patient with aortic regurgitation (−11 mm. Hg). In the other cases these figures generally agreed except for slight and relatively unimportant differences.
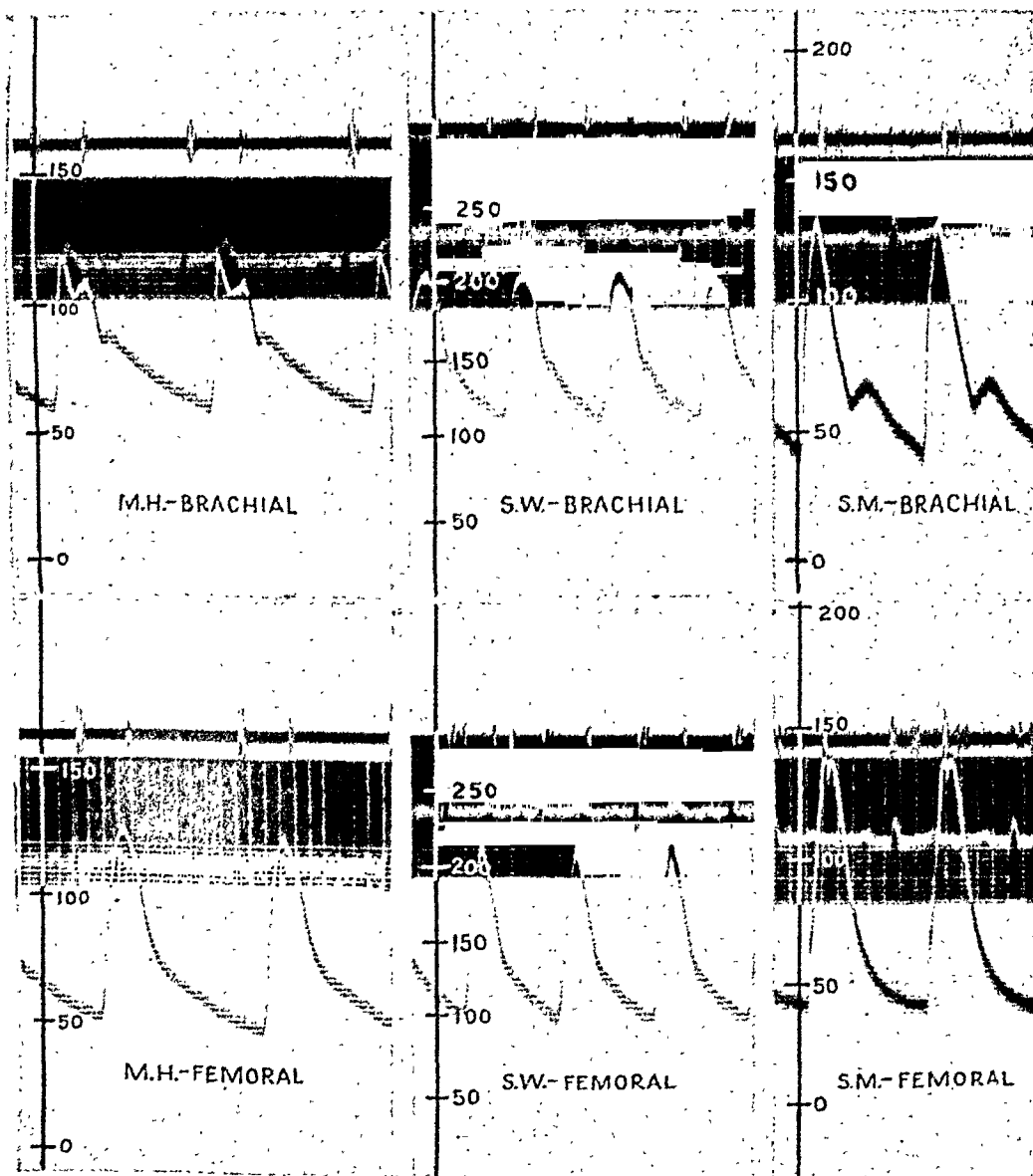
Fig. 1.—Pulse curves of subjects with normal pressure, hypertension, and aortic regurgitation, reading from left to right. The apices of the curves have been retouched for greater clarity in reproduction. The electrocardiogram and heart sounds are also shown.

The form of the brachial and femoral curves is shown in Fig. 1. In general, the contour of these curves is similar to those described by Wiggers,[12] Wolf and von Bonsdorff,[4] Hamilton, et al.,[5] and others. When the pulse curves of all patients were plotted on a common

time versus pressure graph, seven patients with aortic regurgitation showed a steeper upstroke than the control or hypertensive group. The other three records of patients with aortic regurgitation showed considerable spread, overlapping with those of the normotensive and hypertensive patients. The dicrotic notch (incisura), which was usually well marked in most brachial records of patients with aortic regurgitation, always appeared at a lower point on the catacrotic limb in these subjects than in those of the control and hypertensive group. However, we were unable to associate a low dicrotic notch with a low diastolic blood pressure or the height of the pulse pressure, indicating that the position and characteristics were probably influenced largely by the peripheral factors which alter plus contours.

DISCUSSION

The accuracy of the method of measuring blood pressure by arterial puncture with a small needle and by optical recording with a high frequency manometer seems to have been generally accepted. It effectively overcomes the objection against cannulation methods of blood pressure measurement, as discussed by Wolf and Bonsdorff[4] and Recklinghausen.[2]

Little apparent change in blood pressure resulted from insertion of the needle into the artery, for cuff measurements on the same arm with the needle in situ showed the same values as before insertion. In agreement with Ragan and Bordley,[7] we noted during deflation of the cuff that the Korotkow sounds appeared at the same moment as the initial manometric pulsations from the artery. Wolf and Bonsdorff[4] felt that considerable differences in pressure might occur between these events.

In these experiments, simultaneous graphic recordings were not made from the femoral and brachial arteries because of technical difficulties. Moreover, the blood pressure readings by the cuff method were not made at the same moment as the graphic ones. However, cuff and direct measurements of blood pressure were always made on the same extremity, whereas previous investigators have used one extremity for direct readings and the opposite for indirect measurements. Appreciable differences may exist between cuff measurements from the two arms. Any unusual weighting of results was believed to have been avoided by making graphic measurements alternately, as follows: first in the arm of one subject and first in the leg of the succeeding one. The relatively small difference in pulse rates between the times of making direct measurements in the arm and leg indicates that little change in cardiovascular function occurred to influence the reliability of the comparison of such values.

In agreement with others who compared the accuracy of the auscultatory method with direct measurements in the arm, we found no consistency in the direction of error, either in the systolic or

diastolic levels; the auscultatory readings were sometimes too high, and sometimes too low. However, the averaged errors permit the conclusion that, for general clinical purposes, the auscultatory technique is adequate for the brachial systolic level, provided results in any given case are not interpreted too rigidly. No particular difference in degree of accuracy was found in brachial measurements of systolic pressures in the control or hypertensive groups, or in patients with aortic regurgitation. The diastolic cuff pressures were ascertained less accurately in the arm. Values taken when the arterial sounds changed from sharp to muffled (between third and fourth phases) were generally too high, and the error was of the same degree in the normotensive and hypertensive groups. As one would expect, the error was greater in aortic regurgitation, in which the sound changes are often less marked. Since, to simplify the technique of puncture of the brachial artery, we purposely excluded subjects with large arms, we do not feel that this source of error in cuff measurements enters into the differences.

The standard cuff (13 cm.) technique for femoral pressure was found to be deceptive in almost all subjects; it gave readings which were grossly too high. The wide cuff (15.5 cm.) pressures generally agreed better with direct pressures, although there was still considerable error in many measurements; this error was most marked in patients with aortic regurgitation. Since, in general, the graphic systolic blood pressures in the leg tended to be only slightly higher than those in the arm, the larger differences obtained by either cuff are therefore inferred to be artifacts. The greater mass of soft tissue to be compressed, as well as other anatomic differences, seems to be responsible, for more accurate results can be obtained by a better fitting, wide cuff.

The width (12 to 13 cm.) of the present standard arm cuff is based on the observations of Recklinghausen[2] and Janeway,[12] who recognized that the soft tissue distorts the actual pressure applied to an artery when a narrower cuff (such as Riva-Rocci's) is used. Their choice of the 13 cm. cuff for use on the arm was based on their observation that, with it, approximately the same pressures could be obtained in the leg as in the arm; we could not confirm this observation. For extreme cases they found a wider (15 cm.) cuff adequate for any extremity. Recently, Hamilton and his associates, using children as subjects, and Ragan and Bordley, using adults, recognized the errors from the use of arm cuffs of improper width, and showed that, in general, the width of the cuff should be proportionate to the circumference of the arm. Murray[14] was the first (1914) to report the use of a wider (17 cm.) cuff for femoral pressures. Since then wider cuffs have often been recommended for use on the thigh, but, thus far, there have been no attempts to test their accuracy by comparison with a valid direct method.

The concept that the systolic pressure is higher in the femoral artery in aortic regurgitation originated in 1909 with Hill, et al.,[15] who observed by the palpatory method, with the cuff wrapped around the calf, marked elevation of this pressure over the pressure in the arm. The difference was not limited to aortic insufficiency, for similar discrepancies were noted after excitement and exercise in normal subjects. Murray confirmed this observation, using the 17 cm. cuff. Since then the clinical concept has grown that a higher systolic pressure in the leg is a characteristic, almost specific, sign in aortic regurgitation. In fact, Loewenberg[16] stated that the differentiation between "relative" and true aortic regurgitation may be made on the absence or presence of this sign. This appears to be erroneous because the usual leg cuff will distort the true pressures, and because the true femoral systolic blood pressure is not universally or exclusively higher in definite aortic regurgitation.

Many of the earlier investigators believed that the systolic blood pressure was the same in the arm and leg in normal subjects. On this assumption von Recklinghausen and Janeway based their philosophy of clinical sphygmomanometry. However, Bazett,[17] using one of the cruder membrane manometers, showed that the systolic pressure in the femoral artery was slightly higher than that in the carotid artery in normal dogs. When aortic regurgitation was artificially produced in these animals, the difference was immediately exaggerated, and grew more marked the greater the aortic leak. Burdick and his co-workers,[18] using a 20 cm. cuff for leg measurements, found the femoral systolic pressure moderately higher than the brachial in normal human subjects. Several theories have been advanced to explain these differences in normal subjects and patients with aortic regurgitation. Hürthle[19] believed that the higher systolic pressure in the femoral artery was due to summation of the primary pulse wave and reflected waves from the periphery and from other neighboring vessels. L. Hill and his co-workers[15] attributed the difference to better conduction of the pulse wave into the femoral vessels and to decreased distensibility of the femoral artery. Bazett[17] felt that there was greater conversion of kinetic energy into stress in the femoral artery because of regional differences. Bramwell and Hill[20] believed that "breaker" phenomena at the peak of the onrushing wave front of the pulse were responsible for the greater difference in aortic regurgitation. It is likely that a combination of these factors is responsible.

An attempt was made to correlate the error in the arm cuff readings with the contour of the graphic curves, but no consistent traits in this limited number of subjects were noted. In general, however, the steeper the pulse upstroke in patients with hypertension and aortic regurgitation, the more often the systolic cuff pressures were equal to, or lower than, the direct values. The accuracy of the arm cuff readings was also compared with the Q-E interval (time from onset of

electrical systole to beginning of the upstroke of the brachial pulse curve). As a rule, the Q-E interval was shortest in hypertensive patients (.15 to .18 second), of intermediate duration in normal subjects (.20 to .23 second), and in patients with aortic regurgitation it varied considerably (.15 to .25 second). Since the Q-E interval was essentially the same for the arm and leg at the points where pressure measurements were made, a difference in the velocity of the pulse wave appears not to be a factor in differences between brachial and femoral blood pressures.

SUMMARY

A comparison has been made of the blood pressures measured in the arm and leg with the cuff and usual auscultatory technique and those obtained by direct methods with the needle manometer. The ordinary arm cuff (13 cm. in width) was used for the arm, and this same cuff and a wider (15.5 cm.) one, such as that recommended by the American Heart Association and the Cardiac Society of Great Britain and Ireland, were used for measurements of femoral pressures. Subjects with normal blood pressure, hypertension, and aortic regurgitation were studied.

The cuff pressures in the arm varied both above and below the direct values. As a group, the error was slight for the systolic level, averaging -0.5 per cent, but reached more sizeable proportions for the diastolic pressures of the normotensive and hypertensive groups, in which it was of the order of + 9 per cent. The diastolic cuff error was even greater in subjects with aortic regurgitation, averaging +24 per cent.

The femoral pressures obtained with the 13 cm. cuff on the thigh were grossly above the systolic and diastolic values recorded by the direct method (averaged systolic/diastolic error, normotensive group, $\frac{+17 \text{ per cent}}{+58 \text{ per cent}}$ hypertensive group $\frac{-28 \text{ per cent}}{-46 \text{ per cent}}$; and subjects with aortic regurgitation $\frac{-34 \text{ per cent}}{-92 \text{ per cent}}$). The 15.5 cm. cuff permitted more accurate approximation of the true systolic pressure in the normotensive and hypertensive groups (averaged error, +2.6 per cent, +8 per cent, respectively), but here also the results are in error for the diastolic pressure, averaging +25 per cent for the combined groups. The systolic and diastolic values with the wide cuff on the thigh were most in error in subjects with aortic regurgitation (averaging +29 per cent and +67 per cent, respectively).

The direct femoral systolic blood pressure was notably higher than the direct brachial systolic pressure in five of the nine normotensive subjects, four of the nine hypertensive patients, and seven of the ten patients with aortic regurgitation. In the other cases the difference was slight, although in a few cases the systolic pressures were decidedly

lower in the femoral artery than in the brachial.   The limited number of cases and lack of uniformity of results do not permit any definite conclusion.   However, it may be pointed out that the femoral systolic pressure was more frequently elevated in the patients with aortic regurgitation, and that the differences were usually greater here than in the control and hypertensive groups.

CONCLUSIONS

1. The systolic blood pressure in the arm can be measured with reasonable accuracy in most subjects with normal pressure, hypertension, and aortic regurgitation by the ordinary arm cuff and auscultatory technique.

2. The brachial diastolic pressure, as measured by the ordinary cuff, is usually too high, especially in aortic regurgitation.

3. The femoral systolic blood pressure cannot be measured accurately with the ordinary 13 cm. cuff.   A wider (15.5 cm.) cuff permits more accurate measurement of the femoral systolic pressure, except in subjects with aortic regurgitation whose pressures cannot be measured accurately with either cuff.

4. Femoral diastolic pressures obtained with either cuff were grossly inaccurate in all subjects.

5. The difference between the blood pressure in the arm and leg in patients with aortic regurgitation is not so marked as is generally believed because the cuff, wide or narrow, does not allow true measurements of femoral pressure.   Therefore, it is probable that no diagnostic value should be attributed to this sign.

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THE CARDIAC CHILD IN A SPECIAL SCHOOL

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ONE of the major public health problems concerned with children is that of heart disease which is usually one of the sequelae of rheumatic fever. Although an estimate of the prevalence of rheumatic heart disease is difficult to obtain, Paul[1] states that such an estimate in the United States "would indicate that between 350 and 700 cases exist for every 100,000 people." It is well known that not all attacks of rheumatic fever lead to heart disease. This is a point which many feel has been frequently overlooked. Nevertheless, Swift[2] states: "The seriousness of rheumatic fever to the individual and to large groups of individuals needs no arguing, but there has been less emphasis on the number of patients who have recovered from an acute heart attack without heart involvement, and on the possibility of leading a long, useful and happy life, even wth a certain degree of distortion of the heart valves, if the patient has permanently subdued the rheumatic infection. It would thereby seem only the part of wisdom for society to provide the machinery whereby more patients may be moved to this more fortunate class, even though the rheumatic fever still exists. This would be the objective of an efficient health program."

Although much less frequent than the rheumatic type, other forms of heart disease, such as the congenital type, may also cripple many children. An adequate health program is concerned with educating the child's parents and instructing his teachers, and many authorities agree with Connor[3] that: "A proper regime can be instituted and carried out only by the cooperation of the school teachers, the parents, the physician, the school nurse, the medical social worker, the welfare agencies, housing authorities, and departments of health."

In order to form an estimate of the advantages of sending cardiac children to special schools where, in addition to the normal educational program, emphasis is also placed on instructing the child to live and work with his handicap, we have undertaken a study of cardiac pupils who have attended the Jesse Spalding School of Chicago. The Spalding School is one of four elementary schools (first to eighth grades) and one high school set up by the Public School System of the City of Chicago in 1899. These schools were designed to furnish normal school environment and education for handicapped children, and, as designed, were originally intended to assist crippled children to attend school, primarily

TABLE I

Observations on 186 Children Who Attended Spalding School*

CODE NUMBER	SEX	AGE (YR.)	ON ENTRANCE TO SPALDING		TOTAL YEARS AT SPALDING SCHOOL	ON LEAVING SPALDING		REASON FOR LEAVING SPALDING SCHOOL	NUMBER OF YEARS AFTER LEAVING SPALDING	ON RECHECK PHYSICAL EXAMINATION		MEDICAL CARE			RHEUMATIC RECURRENCES	CARDIAC EPISODES AND/OR OTHER ILLNESSES	JOBS HELD	RECREATION
			DIAGNOSIS	CLASSIFICATION		DIAGNOSIS	CLASSIFICATION			DIAGNOSIS	CLASSIFICATION	WITHIN 3 YEARS	MORE THAN 3 YEARS AGO	NONE				
140	M	12	Recent chorea	E	3	Rh. M. L.	1	No further special school care felt to be necessary	12	Rh. M. L. and S.	IIA	X			1		Soliciting—light manual	Horseback riding, swimming, fishing
133	M	15	Recent rheumatic fever and chorea	E	2	Rh. M. L.	1	Graduated—high school	4	No cardiac pathology‡	E	X					Office work odd jobs attending college	
108	M	10	Potential	F	1	Potential	F	No further special school care felt to be necessary	16	No cardiac pathology	F			X			Odd jobs for family—furnace, etc.	Movies
50	M	10	Chorea	F	2	No organic lesion	F	No further special school care felt to be necessary	12	Rh. M. L. (well-comp.)	I	X					Factory—heavy for 8 yr. Factory—light for 2 yr.	Baseball, dancing, football

Case	Sex	Age	Diagnosis	Class	Yrs	Diagnosis	Class	Disposition	Yrs	Diagnosis	Class				No.	Precipitating	Occupation	Recreation
2	F	13	Potential	F	3	Potential	F	No further special school care felt to be necessary	10	No cardiac pathology	F	X			2 (1 is questionable)	Pregnancy	Light housework	Knitting, sewing, reading, radio, and cards
190	F†	12	Potential	F	3	Potential	F	No further special school care felt to be necessary	5	No cardiac pathology	F	X					Clerical	Dancing skating all athletics
43	F	14	Mitral "regurgitation"	I	½	Mitral "regurgitation"	I	No further special school care felt to be necessary	15	Rh. M. I. and S. (well-comp.)	I	X				Pregnancy	Housework cooking	Movies cooking
1	M	14	Rheumatic fever	I	1	Rh. M. I.	I	No further special school care felt to be necessary	3	No cardiac pathology	F	X					College photography	Photography
156	F	12	Mitral stenosis and chorea	I	1	Potential	F	No further special school care felt to be necessary	15	Mitral "regurgitation," comp. myocardium‡	IIB	X				Pregnancy	Helping in home	Movies, cards, and reading
230	M	10	Rh. M. I.	I	3	Rh. M. I.	I	No further special school care felt to be necessary	17	Rh. M. I.	I		X			Accident	Heavy labor	Baseball bowling
124	F	9	Mitral insufficiency	I	5½	Congenital Pat. D. A.	I	Working	7	Congenital Pat. D. A.	I	X					Light factory work	Skating swimming
20	M	15	Rh. M. I. and S.	IIA	½	Rh. M. I. and S.	I	No further special school care felt to be necessary	12	Rh. M. I. and S. (well-comp.)	I			X			Heavy work 1 yr., light work 2 yr., both work for 2 yr.	Baseball swimming

*Three groups (Out of Town, Unable to Locate, No Cooperation) on whom no follow-up physical signs are available are omitted for the sake of brevity.
†Patients who received psychiatric interview.
‡Examination made by family physican.

TABLE I—CONT'D

CODE NUMBER	SEX	ON ENTRANCE TO SPALDING			TOTAL YEARS AT SPALDING SCHOOL	ON LEAVING SPALDING		SPALDING SCHOOL REASON FOR LEAVING	NUMBER OF YEARS AFTER LEAVING SPALDING	ON RECHECK PHYSICAL EXAMINATION		MEDICAL CARE			RHEUMATIC RECURRENCES	CARDIAC EPISODES AND/OR OTHER ILLNESSES	JOBS HELD	RECREATION
		AGE (YR.)	DIAGNOSIS	CLASSIFICATION		DIAGNOSIS	CLASSIFICATION			DIAGNOSIS	CLASSIFICATION	WITHIN 2 YEARS	MORE THAN 3 YEARS AGO	NONE				
42	M	13	Mitral stenosis	IIA	4	Mitral stenosis	IIA	No further special school care felt to be necessary	12	No cardiac pathology	F	X				"Flu"	Light assembling selling inducted into Army	Baseball
96	M	14	Rh. M. I. and S.	IIA	4	Rh. M. I. and S.	I	No further special school care felt to be necessary	9	Rh. M. I.	I	X				Pneumonia "strep" throat	Light work college	Baseball
139	M	13	Rh. M. I.	IIA	4	Rh. M. I.	I	No further special school care felt to be necessary	3	Rh. M. I. (well-comp.); paroxysmal tachycardia	IIA	X				Attacks of tachycardia	Barber school	Sports radio
152	F	13	Mitral stenosis	IIA	4	Mitral stenosis	IIA	Moved	14	Mitral stenosis	I	X				Appendicitis pregnancy	Clerk light housework	Bowling movies reading
208	M	14	Congenital heart disease	IIA	4	Congenital heart disease	IIA	Moved	5	Congenital heart disease	III		X			Frequent coughs and colds	Light clerical	Reading

No.	Sex	Age	Diagnosis		Class		Diagnosis	Class / Note	Age	Diagnosis	Class			History	Occupation	Recreation
6	F	14	Rh. M. I. and S.	1	IIA	1	Rh. M. I. and S.	IIA No further special school care felt to be necessary	6	Rh. M. I. and S.‡ A. I. and S.	IIB	X		Pregnancy	Cashier, part time	Movies
40	F	16	Rh. M. I. and S.	1	IIA	1	Rh. M. I. and S.	IIA III at home	6	Rh. M. I. and S.	IIA	X		Appendectomy	Housework	Reading girl's club
57	F	15	Rh. M. I. and S.	1	IIA	1	Rh. M. I. and S.	IIA Overage—staying at home	5	Rh. M. I. and S.	IIA	X		"Home in bed" "nervous"	Light factory work	Movies
61	F	14	Rh. M. I. and S.	1	IIA	1	Rh. M. I. and S.	IIA No further special school care felt to be necessary	4	Rh. M. I. (well-comp.)	L	X		Asthma appendicitis	Secretarial	Dancing swimming
207	F	6	Mitral insufficiency	1	IIA	1	Rh. M. I.	I No further special school care felt to be necessary	12	Mitral insufficiency†	L	X		Pregnancy	Housework	Movies
117	M	11	Rh. M. I.	1	IIA	1	Rh. M. I.	IIA No further special school care felt to be necessary	15	Rh. M. I. A. I.	IIB	X	1		Barber	Short wave radio operator radio school
122	M	14	Mitral insufficiency	1	IIA	1	Potential	F No further special school care felt to be necessary	13	Potential	F	X		Pneumonia 4 times	Truck driver	Roller skating
145	F	12	Rh. M. I.	1	IIA	1	Rh. M. I.	IIA No further special school care felt to be necessary	10	Rh. M. I. A. I.	IIA	X		2 pregnancies mastoidectomy	Own housework	Movies auto rides
222	M	15	Rh. M. I.	1	IIA	1	Rh. M. I.	IIA No further special school care felt to be necessary	12	Rh. M. I. and S.	IIA	X		Occasional colds	Light work	Reading, baseball, and ice skating

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No.	Sex	Age	Diagnosis	Class		Diagnosis	Class	Status		Diagnosis	Class				Complication	Occupation	Recreation
63	F†	13	Rh. M. I. and S.	IIA	2	Rh. M. I. and S.	IIA	No further special school care felt to be necessary	5	Rh. M. I and S.	IIA		X			Light housework	Dancing embroidery
58	F	16	Rh. M. I.	IIA	2	Rh. M. I.	I	No further special school care felt to be necessary	6	Rh. M. I.	L	X		3	Miscarriage	House-work	Reading
111	M	15	Rh. M. I. and S.	IIA	2	Rh. M. I. and S. A. I.	IIA	Working	3	Rh. M. I. and S. A. I.	IIB	X		1	Pneumonia	Light factory work (standing)	Dancing
218	F	14	Congenital	IIA	2	Congenital	IIA	Working	3	Congenital—patent interventricular septum	I	X				House-work	Music (voice) sewing
146	M	14	Rh. M. I. and S.	IIA	2	Rh. M. I. and S.	IIA	No further special school care felt to be necessary	12	Rh. M. I. and S.	IIA	X			Pleurisy tonsillectomy	Light factory	Baseball photography
227	M	14	Rh. M. I.	IIA	2	Rh. M. I.	I	No further special school care felt to be necessary	4	Possible heart disease	E		X			Light work in printing office	Violin, art work, and bowling
102	M	14	Rh. M. I. and S. with arrhythmia	IIA	2	Rh. M. I. and S.	IIA	No further special school care felt to be necessary	3	Rh. M. I. and S.	IIA	X			Leg injury	Light office work	Fishing swimming
49	F	15	Rh. M. I. and S. with extra systoles	IIA	2	Rh. M. I. and S. with extra systoles	I	No further special school care felt to be necessary	4	Rh. M. I. and S. with extra systoles	IIA		X			Light office and housework	Movies dancing

TABLE I—CONT'D

CODE NUMBER	SEX	AGE (YR.)	ON ENTRANCE TO SPALDING DIAGNOSIS	CLASSIFICATION	TOTAL YEARS AT SPALDING SCHOOL	ON LEAVING SPALDING DIAGNOSIS	CLASSIFICATION	REASON FOR LEAVING SPALDING SCHOOL	NUMBER OF YEARS AFTER LEAVING SPALDING	ON RECHECK PHYSICAL EXAMINATION DIAGNOSIS	CLASSIFICATION	MEDICAL CARE WITHIN 3 YEARS	MORE THAN 3 YEARS AGO	NONE	RHEUMATIC RECURRENCES	CARDIAC EPISODES AND/OR OTHER ILLNESSES	JOBS HELD	RECREATION
177	F	14	Rh. M. L. and S.	IIA	2	Rh. M. L. and S.	IIA	Overage—staying at home	4	Rh. M. L. and S.	IIA	X				Pneumonia	Light factory work	Dancing baseball
158	M	9	Rh. M. L.	IIA	2	Rh. M. L.	IIA	No further special school care felt to be necessary	8	Rh. M. L.	I	X					Attends optometry school	Reading music
217	F	13	Congenital	IIA	2	Congenital	IIA	No further special school care felt to be necessary	3	Congenital heart disease, Pat. interventricular septum	IIB	X				? "nervous" attacks	Secretarial	Dancing movies
148	F	10	Rh. M. S.	IIA	2	Rh. M. L. and S.	IIA	To parochial school	12	Rh. M. L. and S.	IIB	X					Office work	Church movies
219	F	11	Rh. M. L. and S.	IIA	3	Rh. M. L. and S.	IIA	Left against medical advice	5	Mitral stenosis and "regurgitation"?‡	IIA	X				Pregnancy	Light office work part-time waitress	Reading
42	F	12	Post-diphtheritic heart disease	IIA	3	Post-diphtheritic heart disease	IIA	No further special school care felt to be necessary	5	Mitral and aortic insufficiency and stenosis; Pat. D. A. post-diphtheria and scarlet fever	IIB	X				"Strep" throat, appendectomy	Waitress	Dancing sewing

No.	Sex	Age	Diagnosis	Class	Diagnosis	No.	Class	Disposition	Yrs.	Diagnosis	Class			Auto accident	Vocation	Recreation
155	F	16	Aortic "regurgitation"	IIA	Aortic "regurgitation"	3	IIA	Graduated—high school	9	Rh. M. I. and S. A. I. and S.	X		1	Auto accident	Office work	No time
35	F†	13	Rh. M. I. and S.	IIA	Rh. M. I. and S.	3	I	No further special school care felt to be necessary	4	Rh. M. I.	X	I			Light factory work	Swimming
16	M	12	Rh. M. I. and S.	IIA	Rh. M. I. and S.	3	IIA	No further special school care felt to be necessary	6	Rh. M. I.	X	I			Heavy labor light labor	Mechanics
10	M†	12	Chorea	IIA	Potential	3	F	No further special school care felt to be necessary	5	No cardiac pathology	X	F			Odd jobs college	Mechanics swimming
38	M†	11	Rh. M. I.	IIA	Rh. M. I.	3	IIA	No further special school care felt to be necessary	5	Rh. M. I. and S. A. I. and S.	X	I			Window decorator	Speed boating
79	F	14	Rh. M. I.	IIA	Rh. M. I. and S. (well-comp.)	3	IIA	No further special school care felt to be necessary	7	Rh. M. I. (well-comp.)		IIA	X	1		"26" girl	Dancing
126	M	14	Rh. M. I. and S.	IIA	Rh. M. I. and S.	3	IIA	No further special school care felt to be necessary	3	Rh. M. I. and S.	X	IIA			Sore throat	Light factory work	Baseball
178	F	11	Rh. M. I. and S.	IIA	Rh. M. I. and S.	3	IIB	Moved	13	Rh. M. I. and S.	X	I			Pregnancy	House-work	Movies
221	M	16	Rh. M. I. and S.	IIA	Rh. M. I. and S. A. I.	3	IIB	Working	2	Rh. M. I. and S. A. I. and S.	X	IIA				Light factory work	Baseball
103	F†	14	Rh. M. I. and S.	IIA	Rh. M. I. and S.	4	IIA	Graduated—high school	3	Rh. M. I. and S.	X	IIA				Secretarial	Sewing cooking

TABLE I—Cont'd

CODE NUMBER	SEX	ON ENTRANCE TO SPALDING			TOTAL YEARS AT SPALDING SCHOOL	ON LEAVING SPALDING		REASON FOR LEAVING SPALDING SCHOOL	NUMBER OF YEARS AFTER LEAVING SPALDING	ON RECHECK PHYSICAL EXAMINATION		MEDICAL CARE			RHEUMATIC RECURRENCES	CARDIAC EPISODES AND/OR OTHER ILLNESSES	JOBS HELD	RECREATION
		AGE (YR.)	DIAGNOSIS	CLASSIFICATION		DIAGNOSIS	CLASSIFICATION			DIAGNOSIS	CLASSIFICATION	WITHIN 3 YEARS	MORE THAN 3 YEARS AGO	NONE				
199	M	11	Rh. M. I.	IIA	4	Rh. M. I.	IIA	No further special school care felt to be necessary	6	Rh. M. I.	I	X					Drug-store clerk school	Y.M.C.A. swimming
170	F	14	Mitral insufficiency	IIA	4	Mitral insufficiency	IIA	Overage—staying at home	3	Mitral insufficiency (comp.)	I	X			2	Glaucoma	Light factory work	Baseball swimming
162	F	10	Rh. M. I. and S.	IIA	4	Rh. M. I. and S.	IIA	No further special school care felt to be necessary	3	Rh. M. I. and S.	IIA	X					School	Dancing
100	F†	16	Mitral insufficiency	IIA	5	Mitral insufficiency (well-comp.)	I	Overage—staying at home	7	Rh. M. I. and S. A. I. and S.	IIB	X				Mild thyrotoxicosis, pregnancy	House-work	Reading
198	F†	9	Rh. M. I. and S.	IIA	5	Rh. M. I. and S.	IIA	No further special school care felt to be necessary	7	Rh. M. I.	I	X				Pregnancy	Office work	Social life
189	M	12	Rh. M. I. and S.	IIA	5	Rh. M. I. and S.	IIA	No further special school care felt to be necessary	1	Rh. M. I.	IIA	X					School	Baseball swimming
83	M	10	Rh. M. I. and S.	IIA	5	Rh. M. I. and S.	IIA	No further special school care felt to be necessary	1	Rh. M. I.	I	X					School professional golfing	Clarinet golf

No.	Sex	Age	Diagnosis	Class	No.	Diagnosis	Class	Status	No.	Diagnosis	Class				Illness	Occupation	Recreation
98	M	14	Rh. M.I.	IIA	5	Rh. M.I. A.I.	IIA	Graduated—high school	4	Rh. M.I. and S. A.I.	I	X			Tooth abscess	Tool and die maker	Horse-back riding
107	F	8	Rheumatic mitral "regurgitation"	IIA	5	Rheumatic mitral "regurgitation"	I	No further special school care felt to be necessary	9	Possible heart disease	E	X			Ovarian cyst	House-work	Dancing
37	M	12	Rh. M.S.	IIA	5	Rh. M.I. and S.	IIB	Working	9	Rh. M.I. and S. with extra systoles	IIA	X			Taking digitalis	Barber	Bowling
70	F	12	Rh. M.I.	IIA	5	Rh. M.I.	IIA	No further special school care felt to be necessary	3	Rh. M.I. and S. A.I.	IIA		X		Sore throat	Light factory work	Dancing
80	F	6	Rh. M.I. and S.	IIA	5	Rh. M.I. and S.	IIA	No further special school care felt to be necessary	3	Rh. M.I. and S. A.I. and S.	IIB	X		1		Light factory work	Reading knitting
45	F	13	Rh. M.I. and chorea	IIA	5	Rh. M.I.	IIA	Working	6	Rh. M.I. and S.	IIA	X			Sore throat	Light factory work	Dancing
187	F	13	Rh. M.S.	IIA	6	Rh. M.S.	IIA	Ill at home	9	Rh. M.I. and S.	IIB	X			"Flu"	Office work	Fond of the country
78	F	8	Mitral insufficiency	IIA	7	Mitral insufficiency and stenosis	IIA	No further special school care felt to be necessary	8	Mitral insufficiency	I	X				Light factory work	Music beauty culture
88	Ft	17	Paroxysmal tachycardia; possible congenital	IIA	3	Paroxysmal tachycardia; possible congenital	III	Ill—hospitalized	6	Paroxysmal tachycardia, Pat. D. A.	I	X				Teaches music at home	Piano

TABLE I—Cont'd

CODE NUMBER	SEX	ON ENTRANCE TO SPALDING — AGE (YR.)	DIAGNOSIS	CLASSIFICATION	TOTAL YEARS AT SPALDING SCHOOL	ON LEAVING SPALDING — DIAGNOSIS	CLASSIFICATION	REASON FOR LEAVING SPALDING SCHOOL	NUMBER OF YEARS AFTER LEAVING SPALDING	ON RECHECK PHYSICAL EXAMINATION — DIAGNOSIS	CLASSIFICATION	MEDICAL CARE WITHIN 3 YEARS	MORE THAN 3 YEARS AGO	NONE	RHEUMATIC RECURRENCES	CARDIAC EPISODES AND/OR OTHER ILLNESSES	JOBS HELD	RECREATION
161	M	8	Rheumatic mitral "regurgitation"	IIA	8	Rh. M. I. and S.	IIB	No further special school care felt to be necessary	10	Rheumatic heart disease; auricular fibrillation	III	X			"?"			Photography
90	F	8	Rh. M. I. and S. A.I.	IIA	8	Rh. M. I. and S. A.I.	IIA	No further special school care felt to be necessary	4	Rh. M. I. and S. A. I. and S.	IIA	X					Sedentary assembling	Roller skating
183	F	12	Rh. M. I. and S.	IIB	1	Rh. M. I. and S.	IIB	Transferred—distance to special school too great	9	Rh. M. I. A. I. (well. comp.)	I		X			Pregnancy U.R.I.	House work outside of home	Dancing, ice skating, and swimming
191	F	16	Rh. M. I. and S. A. I. and S.	IIB	1	Rh. M. I. and S. A. I. and S.	IIA	Working	13	Rh. M. I. A. I. (well. comp.)	IIA	X			1	3 full-time pregnancies, 2 miscarriages	House work care of children	Roller skating
187	M	10	Mitral stenosis	IIB	1	Mitral stenosis	IIA	No further special school care felt to be necessary	18	Rh. M. I. A. I. (well. comp.)	I	X				"Bronchial trouble" needs x-ray	Heavy labor	Tumbling boxing

No.	Sex	Age	Diagnosis	Class	Int.	Diagnosis	Class	Disposition	Int.	Diagnosis	Class	X			Occupation	Recreation
54	F	11	Rheumatic heart disease chorea	IIB	1	Rheumatic heart disease	IIA	No further special school care to be necessary	12	Rh. M.I.	I	X			House-work	Walking
101	M	15	Rh. M.I. and S.	IIB	1	Rh. M.I. and S.	IIA	No further special school care felt to be necessary	10	Rh. M.I. and S. A.I. and S.	IIB	X		Stomach trouble	Heavy labor	Photography
15	M	13	Rh. M.I. and S.	IIB	1	Rh. M.I. and S.	IIB	No further special school care felt to be necessary	18	Rh. M.I. and S.	I	X		Operation	Light work	Photography
19	M†	16	Rh. M.I. and S. A.I.	IIB	1½	Rh. M.I. and S. A.I.	IIB	Left against medical advice	7	Rh. M.I. and S. A.I.	IIA	X		Occasional cold	Light work	Handy about the house
81	M	16	Rh. M.I. and S.	IIB	2	Rh. M.I. and S.	IIB	Dismissed—municipal tuberculosis sanitarium. (Pulmonary tuberculosis)	6	Rh. M.I.‡	IIA	X		Dementia praecox	None	None
209	M	14	Congenital interventricular septal defect	IIB	2	Congenital interventricular septal defect	IIA	No further special school care felt to be necessary	6	Congenital	IIA	X			Light work	Bowling
165	M	17	Rh. M.I. and S. A.I.	IIB	2	Rh. M.I. and S. A.I.	IIB	Ill at home	6	Rh. M.I. and S. A.I.	IIB	X		Occasional cold and sore throat	Light work	Stamp collecting bowling
71	M	12	Rh. M.I. and S.	IIB	2	Rh. M.I. and S.	IIB	No further special school care felt to be necessary	18	Rheumatic pancarditis; decompensation; auricular fibrillation‡	III	X	1	In the hospital at the time	Traveling salesman	Not known

TABLE I—CONT'D

CODE NUMBER	SEX	ON ENTRANCE TO SPALDING			TOTAL YEARS AT SPALDING SCHOOL	ON LEAVING SPALDING		REASON FOR LEAVING SPALDING SCHOOL	NUMBER OF YEARS AFTER LEAVING SPALDING	ON RECHECK PHYSICAL EXAMINATION		MEDICAL CARE			RHEUMATIC RECURRENCES	CARDIAC EPISODES AND/OR OTHER ILLNESSES	JOBS HELD	RECREATION
		AGE (YR.)	DIAGNOSIS	CLASSIFICATION		DIAGNOSIS	CLASSIFICATION			DIAGNOSIS	CLASSIFICATION	WITHIN 3 YEARS	MORE THAN 3 YEARS AGO	NONE				
134	M	16	Hypertension, cardiorenal, vascular type	IIB	2	Hypertension cardiorenal vascular type	IIB	No further special school care felt to be necessary	?	Hypertension	E	X					Light work	Sports reading
188	M	14	Rh. M. I. and S. A. I.	IIB	2	Rh. M. I. and S. A. I.	IIB	No further special school care felt to be necessary	3	Rh. M. I. and S. A. I. and S.	IIB	X			?	"Flu"	Light work	Reading
25	F	13	Rh. A. I.	IIB	3	Rh. A. I.	IIA	No further special school care felt to be necessary	?	Rh. A. I.	IIA	X					School	Dancing reading
30	F	12	Rh. M. I. and S. A. I.	IIB	3	Rh. M. I. and S. A. I.	IIB	No further special school care felt to be necessary	2	Rh. M. I. and S. A. I. and S.	IIA	X					Light work	Sewing beauty culture
82	M	15	Congenital	IIB	3	Congenital	IIB	Working	15	Congenital	IIB	X				"Strep" infection pleurisy	Heavy work	Movies reading
87	M	15	Rh. M. I. and S. A. I. and S.	IIB	3	Rh. M. I. and S. A. I. and S.	IIB	Working	4	Rh. M. I. and S. A. I. and S.	IIA	X			?		Heavy work	Art work baseball

No.	Sex	Age	Diagnosis	Class	Yrs	Diagnosis	Class	Disposition	Yrs	Diagnosis	Class	X	No.	Remarks	House-work	Swimming
95	F	16	Rh. M. I. and S.	IIB	2	Rh. M. I. and S.	IIA	Working	7	Rh. M. I. and S. (well-comp.)	I	X		Appendectomy	House-work	Swimming
114	F†	14	Rh. M. I.	IIB	3	Rh. M. I.	IIA	Overage—staying at home	7	No cardiac pathology†	F	X		4 pregnancies	House-work	Movies
136	F	13	Rh. M. I. and S.	IIB	3	Rh. M. I. and S.	IIB	Ill—hospitalized	5	Rh. M. I. and S.	IIA	X	10	Operation	None	Hand-work
169	M	15	Rh. M. I. and S.	IIB	3	Rh. M. I. and S.	IIB	Moved	6	Rh. M. I. and S.; A. I.	IIA	X		Psychotic	Light work	Photography
173	M	15	Rh. M. I. and S. A. I. and S.	IIB	3	Rh. M. I. and S. A. I. and S.	IIB	No further special school care felt to be necessary	4	Rheumatic heart disease; auricular fibrillation	IIB	X	2		Light work	Printing
184	M	14	Rh. M. I. and S. A. I. and S.	IIB	3	Rh. M. I. and S. A. I. and S.	IIB	Left against medical advice	5	Rh. M. I. and S. A. I.	IIA	X			Light work	Assistant scout-master dancing
213	F	11	Rh. M. I. and S.	IIB	3	Rh. M. I. and S.	IIA	Graduated—high school	14	Rh. M. I. and S.	IIA	X			High school	Baseball hockey swimming
17	F	12	Rh. M. I. and S.	IIB	4	Rh. M. I. and S.	IIB	Graduated—high school	3	Rheumatic heart disease; auricular fibrillation	III	X	2	Accident	School	Dancing
77	F†	11	Congenital patent interventricular septum	IIB	4	Congenital Pat. D. A.	IIB	No further special school care felt to be necessary	5	Congenital, Pat. D. A.	I				Light work	Piano dancing

TABLE I—CONT'D

CODE NUMBER	SEX	AGE (YR.)	ON ENTRANCE TO SPALDING		TOTAL YEARS AT SPALDING SCHOOL	ON LEAVING SPALDING		REASON FOR LEAVING SPALDING SCHOOL	NUMBER OF YEARS AFTER LEAVING SPALDING	ON RECHECK PHYSICAL EXAMINATION		MEDICAL CARE			RHEUMATIC RECURRENCES	CARDIAC EPISODES AND/OR OTHER ILLNESSES	JOBS HELD	RECREATION
			DIAGNOSIS	CLASSIFICATION		DIAGNOSIS	CLASSIFICATION			DIAGNOSIS	CLASSIFICATION	WITHIN 3 YEARS	MORE THAN 3 YEARS AGO	NONE				
105	M	10	Rh. M. L. and S.	IIIB	4	Rh. M. L. and S.	IIA	No further special school care felt to be necessary	3	Rh. M. L. (well-comp.)	I	X			2		School light work	Baseball singing
110	F	11	Rh. M. L. and S.	IIIB	4	Rh. M. L. and S.	IIA	No further special school care felt to be necessary	3	Rh. M. L. and S.	IIA	X				"Flu"	School light work	Swimming
171	F	11	Rh. M. L. and S.	IIIB	4	Rh. M. L. and S.	IIA	No further special school care felt to be necessary	4	Rh. M. L. and S.	IIA	X					School light work	Singing
172	M	14	Rh. M. L. and S. A. I.	IIIB	4	Rh. M. L. and S. A. I.	IIA	Graduated—high school	2	Rh. M. L. and S. A. I.	IIA	X					School light work	Bowling
93	M	11	Rheumatic mitral "regurgitation"	IIIB	11	Rheumatic mitral "regurgitation"	IIA	No further special school care felt to be necessary	4	Rh. M. L. with extra systoles	IIA	X				Overdigitalization	School	Photography
138	M	12	Rheumatic endocarditis	IIIB	4½	Rheumatic endocarditis	IIIB	No further special school care felt to be necessary	9	No cardiac pathology†	F	X				Occasional tachycardia	Not known	Not known
31	F	11	Rh. M. L. and S.	IIIB	5	Rh. M. L. and S.	IIA	Graduated—high school	2	Rh. M. L. and S.	IIA	X			1 (in bed 1 yr.)	Taking digitalis now	None	Movies

No.	Sex	Age																Work	Hobby
66	M	13	Rh. M. I. and S.	IIB	5	Rh. M. I. and S.	IIA	Graduated—high school	4	Rh. M. I. and S. (well-comp.)	I	X						Medium work	Fishing
113	F	10	Congenital with superimposed Rh. I. and S.	IIB	5	Rh. M. I. and S.	IIA	Overage—staying at home	4	Rh. M. I. and S. A. I.	IIA	X				Cyst operation		Light work	Dancing
128	M†	14	Rheumatic auricular fibrillation	IIB	6	Rh. M. I. and S.	IIB	Graduated—high school	6	Rh. M. I. and S. A. I.	IIA	X				Nasal operation		Light work	Reading
151	F	13	Rh. M. I. and S.	IIB	6	Rh. M. I. and S.	IIA	Graduated—high school	4	Rh. M. I. and S. A. I. and S.	IIB	X			2 (in bed 1 yr.)	Pneumonia, accident		House-work	Radio cooking
159	M†	12	Rh. M. I. and S.	IIB	6	Rh. A. I.	IIA	No further special school care felt to be necessary	5	Rh. M. I.	I	X				Appendicitis, hernia		Light work	Reading radio
181	M†	16	Rh. A. I.	IIB	2	Rh. A. I.	IIB	Working	7	Rh. M. I. and S. A. I.	IIA	X			1			Medium work	Stamp collecting bowling
220	M	11	Rheumatic mitral "regurgitation" and stenosis	IIB	6	Rheumatic mitral "regurgitation" and stenosis	IIB	Overage—staying at home	3	Rh. M. I. and S. A. I.	IIB	X						Light work	Baseball
55	M	11	Rh. M. I. and S.	IIB	6	Rh. M. I. and S.	IIA	No further special school care felt to be necessary	1	Rh. M. I. (well-comp.)	I	X					School		Baseball

TABLE 1—CONT'D

CODE NUMBER	SEX	ON ENTRANCE TO SPALDING			TOTAL YEARS AT SPALDING SCHOOL	ON LEAVING SPALDING		REASON FOR LEAVING SPALDING SCHOOL	NUMBER OF YEARS AFTER LEAVING SPALDING	ON RECHECK PHYSICAL EXAMINATION		MEDICAL CARE			RHEUMATIC RECURRENCES	CARDIAC EPISODES AND/OR OTHER ILLNESSES	JOBS HELD	RECREATION
		AGE (YRS.)	DIAGNOSIS	CLASSIFICATION		DIAGNOSIS	CLASSIFICATION			DIAGNOSIS	CLASSIFICATION	WITHIN 3 YEARS	MORE THAN 3 YEARS AGO	NONE				
25	F	14	Rh. M. L. and S.	IIB	6	Rh. M. L. and S.	IIB	Graduated—high school	6	Rheumatic heart Disease‡	IIB	X				Pregnancy	House-work	Sewing
176	F	8	Rh. M. L. and S.	IIB	6	Rh. M. L. and S.	IIA	No further special school care felt to be necessary	1	Rh. M. L. and S.	IIB	X			1		School	Piano
180	M	11	Rh. M. L. and S.	IIB	6	Rh. M. L. and S.	IIA	No further special school care felt to be necessary	1	Rh. M. L. and S.	IIB	X					Trade school	Accordion baseball
206	M	10	Rh. M. L. and S. A. L.	IIB	6	Rh. M. L. and S. A. L.	IIA	No further special school care felt to be necessary	1	Rh. M. L. and S. A. L.	IIA	X				Pneumonia	Light work	Baseball
231	F	10	Rh. M. L. and S.	IIB	6	Rh. M. L. and S.	IIB	No further special school care felt to be necessary	3	Rh. M. L. and S.	IIB	X				T. & A.	Light work	Tennis
182	F	8	Congenital	IIB	7	Congenital	IIB	No further special school care felt to be necessary	9	Congenital	IIB	X				Dizziness	Light work	Movies radio

Case	Sex	Age	Diagnosis	Class	Age	Diagnosis	Class	Disposition	No.	Diagnosis	Class				Intercurrent illness	Occupation	Hobby
12	M	8	Rh. M.I. A.I.	IIB	7	Rh. M.I. and S. A.I.	IIB	Moved	8	Rh. M.I. and S. A.I. and S.	IIB	X				Medium work	Skiing travel
125	M	9	Rh. M.I. A.I.	IIB	7	Rh. M.I. A.I.	IIB	No further special school care felt to be necessary	5	Rh. M.I. and S. A.I. and S.	IIB	X		1	Colds	Medium work	Movies
232	M	13	Congenital	IIB	7	Congenital	IIB	Graduated—high school	3	Congenital patent interventricular septal defect	IIA	X			"Streptococcal grippe"	School light work	Art work
116	F	8	Rh. M.I. and S.	IIB	8	Rh. M.I. and S.	IIB	Overage—staying at home	3	Rh. M.I. and S. A.I.	IIB	X			Gall bladder attacks	Light work	Dancing movies
46	M	9	Rh. M.I. and chorea	IIB	9	Rh. M.I.	IIA	No further special school care felt to be necessary	3	Rh. M.I. and S.	IIA	X				Trade school	Baseball
167	F	8	Rh. M.S.	IIB	9	Rh. M.I. and S.	IIA	Working	8	Rh. M.I. and S. with extra systoles	IIA	X			"Cyst of back" pregnancy	House-work	Sewing
27	F	10	Rh. M.I. and S.	IIB	10	Rh. M.I. and S.	IIB	Graduated—high school	4	Rheumatic mitral lesion; auricular fibrillation‡	IIB	X		1		Light work	Sewing reading
135	M	7	Rh. M.I. and S.	IIB	11	Rh. M.I. and S.	IIB	No further special school care felt to be necessary	9	Rh. M.I. and S.	IIA	X			U.R.I.	Medium work	Photography
179	M	7	Rh. M.I. and S. A.I. and S.	IIB	11	Rh. M.I. and S. A.I. and S.	IIB	Graduated—high school	7	Rh. M.I. A.I.‡	IIB	X			U.R.I.	Not known	Not known

TABLE I—CONT'D

CODE NUMBER	SEX	ON ENTRANCE TO SPALDING			TOTAL YEARS AT SPALDING SCHOOL	ON LEAVING SPALDING		REASON FOR LEAVING SPALDING SCHOOL	NUMBER OF YEARS AFTER LEAVING SPALDING	CAUSE OF DEATH COPIED FROM DEATH CERTIFICATE	AUTOPSY	AGE AT DEATH
		AGE (YR.)	DIAGNOSIS	CLASSIFICATION		DIAGNOSIS	CLASSIFICATION					
216	F	9	Mitral insufficiency and stenosis	I	4	Mitral insufficiency and stenosis	I	No further special school care felt to be necessary	11	Subacute bacterial endocarditis; rheumatic heart disease		24
132	M	14	Congenital heart disease	IIA	½	Congenital pulmonary stenosis	IIA	Left against medical advice	2	Morbus caeruleus, impotency of foramen ovale		16½
168	F	15	Organic heart disease	IIA	1	Organic heart disease	IIA	No further special school care felt to be necessary	1	Mitral stenosis and regurgitation		17
211	M	9	Mitral insufficiency and stenosis; post-scarlatinal	IIA	1	Mitral insufficiency and stenosis; post-scarlatinal	III	Ill at home	1			11
174	M	11	Mitral insufficiency and stenosis; aortic insufficiency	IIA	1	Mitral insufficiency and stenosis; aortic insufficiency	IIA	No further special school care felt to be necessary	9			21
112	F†	14	Congenital heart disease; interventricular septal defect	IIA	2	Congenital heart disease; interventricular septal defect	IIA	Overage—staying at home	4	Malignant endocarditis	X	20
147	M†	11	Rh. M. I.	IIA	2	Rh. M. I. and S.	IIA	No further special school care felt to be necessary	3	Chronic myocarditis		16
118	M	10	Rh. M. I. and S.	IIA	2½	Rh. M. I. and S.	IIA	Ill at home	11	Inactive rheumatic heart disease with M. I. and S. A. I. and S.		23½

TABLE I—CONT'D

CODE NUMBER	SEX	ON ENTRANCE TO SPALDING			TOTAL YEARS AT SPALDING SCHOOL	ON LEAVING SPALDING		REASON FOR LEAVING SPALDING SCHOOL	NUMBER OF YEARS AFTER LEAVING SPALDING	CAUSE OF DEATH COPIED FROM DEATH CERTIFICATE	AUTOPSY	AGE AT DEATH
		AGE (YR.)	DIAGNOSIS	CLASSIFICATION		DIAGNOSIS	CLASSIFICATION					
5	M	7	Mitral insufficiency and stenosis	IIA	3	Mitral insufficiency and stenosis	III	Ill at home	2	Chronic myocarditis with ascites		12
9	M	9	Rh. M. I. and S.	IIA	3	Rh. M. I. and S.	IIA	No further special school care felt to be necessary	11			23
64	F	8	Rh. M. I.	IIA	3	Rh. M. I. and S.	IIA	No further special school care felt to be necessary	6	Rheumatic heart disease		17
84	F	14	Mitral insufficiency and stenosis	IIA	3	Rh. M. I. and S. A. I.	IIA	Working	3	Acute bacterial endocarditis		20
56	M	13	Rh. M. I. and S. A. I. and S.	IIA	3½	Rh. M. I. and S. A. I. and S.	IIB	Ill at home	1	Chronic rheumatic endocarditis and myocarditis		17½
183	F	14	Congenital heart disease	IIA	3½	Congenital heart disease	IIA	Working	8			25½
186	F	9	Rh. M. I. and S.	IIA	3½	Rh. M. I. and S.	III	Ill—hospitalized	1	Mitral stenosis and regurgitation; rheumatic endocarditis		13½
215	F	10	Mitral insufficiency and stenosis	IIA	4	Mitral insufficiency and stenosis	IIA	Moved	4	Chronic endocarditis; myocarditis		18
119	F†	14	Rh. M. I. and S.	IIA	4	Rh. M. I. and S.	IIA	Graduated— high school	7	Acute cardiac failure; rheumatic endocarditis	X	25
144	M	7	Mitral insufficiency and stenosis	IIA	4	Mitral insufficiency and stenosis	IIA	No further special school care felt to be necessary	8	Rheumatic heart disease; double mitral and aortic lesions		19

TABLE I—CONT'D

| CODE NUMBER | SEX | ON ENTRANCE TO SPALDING | | | TOTAL YEARS AT SPALDING SCHOOL. | ON LEAVING SPALDING | | REASON FOR LEAVING SPALDING SCHOOL | NUMBER OF YEARS AFTER LEAVING SPALDING | CAUSE OF DEATH COPIED FROM DEATH CERTIFICATE | AUTOPSY | AGE AT DEATH |
		AGE (YR.)	DIAGNOSIS	CLASSIFICATION		DIAGNOSIS	CLASSIFICATION					
212	F	10	Mitral insufficiency and stenosis	IIA	4	Rh. M. I. and S. A. I. and S.	III	Ill—hospitalized	½	Mitral insufficiency and stenosis; cardiac hypertrophy and dilatation		14½
74	M	11	Rh. M. I. and S.	IIA	4½	Rh. M. I. and S.	IIA	Ill at home	9			24½
7	M	10	Mitral insufficiency and stenosis	IIA	7	Rh. M. I. and S.	IIA	Overage—staying at home	2	Rheumatic heart disease		19
8	F	9	Organic heart disease	IIB	½	Organic heart disease	IIB	No further special school care felt to be necessary	2			11½
86	F	8	Rh. M. I.	IIB	½	Rh. M. I. and S.	IIB	Ill at home	5	Chronic valvular heart disease with acute exacerbation; acute articular rheumatism		13½
154	F	15	Rheumatic myocarditis	IIB	½	Rheumatic myocarditis	IIB	Ill at home	1	Rheumatic heart disease with mitral stenosis; regurgitation pericarditis		16½
201	F	15	Rh. M. I. and S. A. I.	IIB	½	Rh. M. I. and S. A. I.	III	Ill at home	1			16½
205	M	15	Rh. M. I. and S.	IIB	½	Rh. M. I. and S.	IIB	Left against medical advice	3			18½
14	M	15	Rh. M. I. and S.	IIB	1	Rh. M. I. and S. A. I.	III	Ill—hospitalized	1	Rheumatic heart disease with double mitral and double aortic		17

TABLE I—CONT'D

| CODE NUMBER | SEX | ON ENTRANCE TO SPALDING | | | TOTAL YEARS AT SPALDING SCHOOL | ON LEAVING SPALDING | | REASON FOR LEAVING SPALDING SCHOOL | NUMBER OF YEARS AFTER LEAVING SPALDING | CAUSE OF DEATH COPIED FROM DEATH CERTIFICATE | AUTOPSY | AGE AT DEATH |
		AGE (YR.)	DIAGNOSIS	CLASSIFICATION		DIAGNOSIS	CLASSIFICATION					
32	F	16	Rh. M. I.	IIB	1	Rh. M. I. and S.	IIB	Ill at home	1	Terminal lobar pneumonia; chronic rheumatic endocarditis with cor bovinum		18
97	F	14	Rh. M. I. and S.	IIB	1	Rh. M. I. and S.	IIB	Ill at home	1	Organic heart disease; acute pulmonary edema		16
99	M†	16	Rh. M. I. and S. A. I.	IIB	1	Rh. M. I. and S. A. I. and S.	IIB	Graduated— high school	4	Subacute bacterial endocarditis with multiple infarcts in kidneys and spleen		21
143	M	13	Congenital heart disease	IIB	1	Congenital heart disease	IIB	Moved	3	Rheumatism endocarditis		17
160	F	13	Rh. M. I. and S.	IIB	1	Rh. M. I. and S.	III	Ill at home	3	Decompensation mitral stenosis		17
224	F	9	Rh. M. I. and S.	IIB	1	Rh. M. I. and S.	IIB	Transferred— distance to special school too great	3			13
34	M	13	Rh. M. I. and S. A. I.	IIB	2	Rh. M.I. and S. A. I. and S.	IIB	Moved	2	Chronic endocarditis		17
72	F	13	Rh. M. I. Congenital	IIB	2	Congenital with superimposed Rh. M. I. and S. A. I.	IIB	Left against medical advice	4	Cerebral embolus, endocarditis, and pleurisy		19
129	F	16	Organic heart disease	IIB	2	Organic heart disease	III	Ill at home	Date unknown			

TABLE I—CONT'D

CODE NUMBER	SEX	ON ENTRANCE TO SPALDING			TOTAL YEARS AT SPALDING SCHOOL	ON LEAVING SPALDING		REASON FOR LEAVING SPALDING SCHOOL	NUMBER OF YEARS AFTER LEAVING SPALDING	CAUSE OF DEATH COPIED FROM DEATH CERTIFICATE	AUTOPSY	AGE AT DEATH
		AGE (YR.)	DIAGNOSIS	CLASSIFICATION		DIAGNOSIS	CLASSIFICATION					
157	M	14	M. I. and S. A. I. and S.	IIB	2	M. I. and S. A. I. and S.	IIB	Working	9	Mitral regurgitation; chronic articular rheumatism		25
192	F	9	Mitral "regurgitation"	IIB	2	M. I. and S.	III	Ill at home	2	Valvular heart disease with decompensation; acute endocarditis		13
18	M	8	Rh. M. I. and S.	IIB	3	Rh. M. I. and S.	IIB	Moved	2	Chronic myocarditis		13
68	M	14	Rh. M. I. and S. A. I. and S.	IIB	3	Rh. M. I. and S. A. I. and S.	IIB	Graduated— high school	2	Rheumatic heart disease		19
76	M	14	Rh. M. I. and S.	IIB	3	Rh. M. I. and S.	IIB	Moved	1	Lobar pneumonia		18
202	F	13	Rh. M. I. and S.	IIB	3	Rh. M. I. and S.	IIB	Overage— staying at home	4			20
203	F	14	Mitral insufficiency	IIB	3	Mitral insufficiency and stenosis	IIB	Overage— staying at home	3			20
233	M	12	Congenital heart disease	IIB	3	Congenital heart disease	IIA	No further special school care felt to be necessary	4			19
21	F	12	Rh. M. I. and S.	IIB	4	Rh. M. I. and S.	IIB	Ill at home	2	Endocarditis nephritis		18
28	F	13	Congenital heart disease	IIB	4	Congenital heart disease	IIB	Working	2	Chronic myocarditis		19
59	M	16	Rheumatic pancarditis	IIB	4	Rheumatic pancarditis	IIB	Graduated— high school	2	Chronic rheumatic endocarditis; chronic valvular heart disease		20

TABLE I—CONT'D

CODE NUMBER	SEX	ON ENTRANCE TO SPALDING			TOTAL YEARS AT SPALDING SCHOOL	ON LEAVING SPALDING		REASON FOR LEAVING SPALDING SCHOOL	NUMBER OF YEARS AFTER LEAVING SPALDING	CAUSE OF DEATH COPIED FROM DEATH CERTIFICATE	AUTOPSY	AGE AT DEATH
		AGE (YR.)	DIAGNOSIS	CLASSIFICATION		DIAGNOSIS	CLASSIFICATION					
89	F	9	Rh. M. I. and S.	IIB	4	Rh. M. I. and S.	III	Ill—hospitalized	2	Chronic myocarditis with decompensation; pericarditis (acute)		15
210	M	16	Congenital heart disease	IIB	4	Congenital heart disease	IIB	Graduated—high school	4	Rheumatic heart disease		24
69	F†	14	Congenital heart disease	IIB	5	Congenital heart disease	IIB	Graduated—high school	3	Bacterial endocarditis; congenital heart disease		22
121	M	11	Rh. M. I. and S.	IIB	5	Rh. M. I. and S.	III	Ill at home	2	Rheumatic heart disease		18
185	F	15	M. I. and S. A. I. (post-diphtheritic) (post-scarlet)	IIB	5	M. I. and S. A. I. (post-diphtheritic) (post-scarlet)	IIB	Graduated—high school	2	Cerebral embolism; subacute bacterial endocarditis; rheumatic pancarditis	X	22
204	F	12	M. I. and S.	IIB	5	M. I. and S.	IIB	Working	1	Chronic myocarditis; cardiac decompensation		18
85	M	11	Rh. M. I. and S.	IIB	7	Rh. M. I. and S. A. I.	IIB	Graduated—high school	1 mo.	Rheumatic heart disease with auricular fibrillation; cardiac decompensation; adhesive pericarditis	X	18
104	M	9	Congenital heart disease	IIB	7	Congenital heart disease	IIB	Graduated—high school	2	Streptococcic meningitis; congenital heart malformation		18
191	M†	12	Rh. M. I. and S.	IIB	9½	Rh. M. I. and S.	IIB	Graduated—high school	1½	Chronic myocarditis		23

by the use of elevators, ramps, orthopedic equipment, physiotherapy, swimming pools, etc., even if they required constant medical supervision and treatment. In 1924, through the efforts, and under the supervision, of the Chicago Heart Association, cardiac children were admitted to these schools as a group which formed at that time 13 per cent of the total enrollment, and is now substantially increased.

The eligibility of a child to attend one of these special schools depends upon whether he "by reason of disease, accident or congenital deformity, cannot attend a regular school with safety and profit, during the period of his physical rehabilitation, simultaneous mental development, and social adjustment."[4] The Chicago Heart Association appoints a physician for each school, and, in addition, there is full-time nursing service, originally furnished through the facilities of the Visiting Nurse Association of Chicago, and now through the cooperation of the Board of Health of the City of Chicago. Bus transportation, elevators, ramps, and wheel chairs are provided. The nurses take daily pulse rate and temperature readings, carry out all treatments prescribed by private or clinic physicians, conduct supervised rest periods, make home calls to provide some social service contact, and assist the Chicago Heart Association school physician in controlling the activities of the cardiac child in school.

It must be made clear that the medical management in these cases is left entirely to the private or clinic physician. The Chicago Heart Association school physician examines all children referred for admission, and reserves the right to deny admission to noncardiacs, to those with heart disease in Class I who could undertake ordinary school activity, and to those who are too ill for any school activity. On the other hand, he may admit patients with recent infections in order to prevent possible complications and sequelae. In addition, by frequent re-examinations, he limits the activity of the child by rest periods and by controlling the amount of schoolwork and play. He prescribes no medication, but may send the child home or to a hospital, as indicated. Other communities[5] have followed our example with similar plans.

METHOD OF STUDY

All available records of cardiac children who attended Spalding School served as the basis for this study. The recent records were found to be more comprehensive and complete than those of an earlier date, but all provided sufficient information. A total of 233 cases included in the survey falls into five groups:

130 Completely worked up, with recheck physical examinations (Table I).
56 Deceased since leaving school (Table I).
21 Living out of town.
19 Unable to locate.
7 Refused to cooperate.

Thus, 158 are living and presumably well, and 56 are dead. This leaves the small number of 19 unaccounted for. Of the 158 living and well,

130 were available for study. We reviewed their school records, investigated their families and environment, took complete histories of their health since leaving school, and then did our own physical examinations, so that the physical signs that are dependent on subjective interpretation (such as cardiac murmurs) would vary as little as possible. In addition, 32 patients had previously received a psychiatric interview.*

Fig. 1.—Data primarily on the individual.

The questionnaire used in compiling data consists of five pages:

Page 1. Data primarily on the student (Fig. 1).

Page 2. Family data (Fig. 2).

Page 3. Medical history and results of physical examination on entrance to school, as well as subsequent observations. Here both diagnosis and classification are recorded on first physical examination and upon discharge from school (Fig. 3).

*Conducted by Dr. Paul Schroeder and associates at the Institute for Juvenile Research in Chicago.

Page 4. Current social and economic data secured by home call (Fig. 4).

Page 5. Recheck physical examination done at the office of the Chicago Heart Association by Dr. Arthur F. Abt or Dr. Kate H. Kohn. Twelve recheck physical examinations were done by other physicians because the patients were out of town at the time, or because they were under current care for other medical reasons (Fig. 5).

#2

FAMILY HISTORY

NAME	KIN	AGE	PLACE OF BIRTH	OCCUPATION	WAGE
OTHER MEMBERS IN HOUSEHOLD					

HOME AND NEIGHBORHOOD:

HEALTH OF FAMILY:

ATTITUDE OF FAMILY TOWARD CHILD

FAMILY'S PLAN FOR CHILD

Fig. 2.—Family data.

The Classification of Patients with Diseases of the Heart prepared by the Criteria Committee of the New York Heart Association and adopted by the American Heart Association was used. This classification is referred to throughout this paper because it was used at the time of the early physical examination. It is sometimes referred to as the "first," or "old," classification, as opposed to the "new" one adopted in 1939.[6]

In the course of the study, 494 home calls were made and 520 letters sent.

RESULTS AND DISCUSSION

Two hundred thirty-three cases, the five groups previously mentioned, were studied. There were other cardiac patients in the school during the survey period: thirty-four students who attended for less than one semester, and thirty who died while registered at school; these were not included because their records offered too little information.

MEDICAL   #3

HISTORY:
    OBTAINED FROM CLINIC OR M.D._____

_____

PREVIOUS HISTORY: _____

_____

ILLNESSES WITH DATES:
    SCARLET FEVER _____ TONSILLITIS_____ TONSILLECTOMY___
    MEASLES _____ DIPHTHERIA_____ CHOREA_____

HISTORY OF CONGENITAL H.D. - WHEN FIRST NOTED _____

_____

HOW LONG IS CHILD KNOWN TO HAVE HEART DISEASE_____

WHEN AND BY WHOM NOTED _____

RHEUMATISM - DATE FIRST ATTACK_____SUBSEQUENT ATTACKS_____

PHYSICAL EXAMINATION ON ENTRANCE TO SPALDING SCHOOL

DATE:_____
GENERAL CONDITION
    THROAT_____TEETH_____TONSILS_____EARS____NOSE_____ ,

HEART:
    RATE APEX_____   RADIAL_____
    RHYTHM_____   APEX BEAT_____
    THRILL_____   SIZE _____
    SOUNDS_____   MURMURS_____
    BLOOD PRESSURE_____   URINALYSIS_____
    EKG_____   X-RAY _____

CARDIAC DIAGNOSIS _____

_____

CLASSIFICATION_____OTHER LIMITING DISABILITIES_____

SPECIAL NOTES_____

_____

_____

PROGRESS NOTES _____

_____

Fig. 3.—Medical history and results of physical examination on entrance to school, as well as subsequent observations.

The diagnoses on entrance are tabulated in Table II. Eighty-five per cent had rheumatic heart disease and 9.4 per cent had congenital heart disease. It should be noted that these figures are not comparable to those obtained in studies on large groups of children in public schools, where the incidence of rheumatic heart disease is stated to be 55 per cent,[7] 65 per cent,[8] or 69 per cent[9] of all organic heart disease found in school children. White and Jones's study, in 1928 (referred to by White[10]), showed that rheumatic heart disease constituted 92 per cent, and congenital heart disease, 6 per cent, of all children's heart

disease. The slight discrepancy here can be explained by the fact that physicians seem more likely to seek admission for those children with congenital heart disease, especially when they are cyanotic, than for those with rheumatic heart disease in Class I or IIA. The physician is often willing to allow the parents of children with rheumatic heart disease of Class I or IIA to send them to a regular school. The majority of admissions were in cardiac classification IIA or IIB (Table III). Patients placed in Class III were automatically denied admission, but were allowed to reapply upon improvement.

HOME FOLLOW-UP #4
FAMILY

NAME	KIN	AGE	HEALTH	OCCUPATION	INCOME

HOME:
TYPE OF BUILDING_____ LOCATION OF BUILDING_____
NO. OF ROOMS_____ HOW HEATED_____
RENT OR OWN_____ NEIGHBORHOOD_____

PATIENT

H.S. - SPECIAL_____ COURSE_____ GRADES_____
REGULAR_____

YRS. IN EL. SCHOOL_____ YRS. IN H.S._____
EXTRA CURRICULAR WORK
WHILE IN H.S._____
CAMP EXPERIENCE * WHERE_____ WHEN_____
RECREATION_____
MARRIED_____ CHILDREN_____
TYPE OF WORK DONE SINCE   HOW LONG   WAGES
LEAVING SCHOOL_____

PRESENT JOB, IF ANY_____

APPROX. INC. EARNED PAST YR._____ TRANSPORTATION USED_____

GENERAL HEALTH
ANY ATTACKS OR HOSPITALIZATIONS SINCE GRADUATION, WHEN & WHY_____

                        LATE   IMPROVED   WORSE   SAME
MOST RECENT PHYS. EX._____

CLINIC AND NUMBER_____
or
PRIVATE PHYSICIAN_____

COMMENTS_____

Fig. 4.—Current social and economic data secured by home call.

The average age at entrance was 12 years. Metropolitan Life Insurance Company[11] figures give the age of onset of rheumatic fever at "from 5-9," and the average age of onset of rheumatic heart disease as "after 10." White[10] allows a larger latitude: "between the ages of 4

TABLE II

CARDIAC DIAGNOSIS UPON ENTRANCE TO SPALDING SCHOOL

DIAGNOSIS	CASES WITH FULLY COM- PLETED RECORDS	DIED SINCE LEAVING SCHOOL	OUT OF TOWN	UNABLE TO LOCATE	NO COOPER- ATION	TOTAL
Rheumatic heart disease	116	43	17	15	7	198
Congenital heart disease	10	10	2	1		23
Following diphtheria	1					1
Paroxysmal tachycardia	1					1
Renal hypertension	1					1
Congenital with super- imposed rheumatic heart disease	1					1
Miscellaneous		3	2	3		8
						233

PHYSICAL EXAMINATION

                                                        DATE_____

NAME_____   AGE_____ S M W D SEP._____

ADDRESS_____
  DAYS LOST DUE TO ILLNESS
WHILE AT WORK - HOME_____CON. HOME_____HOSP._____.

NATURE OF ILLNESS_____

NEW SYMPTOMS_____

PHYSICAL EXAMINATION:
  WEIGHT_____HEIGHT_____TEMP._____RESP._____

    GENERAL_____

HEART:
  RATE_____

    APEX_____

    RADIAL_____

  RHYTHM_____

  APEX BEAT_____

  THRILL_____

  SIZE_____

  SOUNDS_____

  MURMURS_____

  BLOOD PRESSURE_____

  EKG_____X-RAY_____

  CARDIAC DIAGNOSIS_____

  _____

  _____CLASSIFICATION_____

LIMITING DISABILITIES AS THEY WOULD AFFECT EMPLOYMENT_____

  _____

  _____

                              PHYSICIAN_____

Fig. 5.—Recheck physical examination done at the office of the Chicago Heart Associa-
tion by Dr. Arthur F. Abt or Dr. Kate H. Kohn.

TABLE III

CARDIAC CLASSIFICATION ON ENTRANCE TO SPALDING SCHOOL

CLASSIFICATION	CASES WITH FULLY COMPLETED RECORDS	DIED SINCE LEAVING SCHOOL	OUT OF TOWN	UNABLE TO LOCATE	NO COOPERATION	TOTAL
E	2			1		3
F	4		1	3		8
I	5	1	3	1		10
IIA	63	20	9	9	6	107
IIB	56	35	8	5	1	105
						233

TABLE IV

NATIONALITY OF FAMILIES

NATIONALITY	CASES WITH FULLY COMPLETED RECORDS	DIED SINCE LEAVING SCHOOL	OUT OF TOWN	UNABLE TO LOCATE	NO CO-OPERATION	TOTAL
American	31	12	9	9	3	64
Assyrian		1				1
Bohemian	5					5
Canadian	1					1
Czechoslovakian	3					3
Danish	1					1
English	2	1				3
German	4	4	1	1		10
Greek	3	1				4
Irish	9	2	2			13
Italian	18	9		1	2	30
Lithuanian	2	2	1			5
Norwegian		1				1
Polish	13	5	2	5	1	26
Russian	17	12	2	2		33
Scotch	2					2
Swedish	1	2				3
Ukranian	1					1
Bohemian-Irish	1					1
Croatian-Hungarian	1					1
Dutch-German	1					1
English-Irish	1					1
French-Austrian	1					1
German-Scotch	1					1
Irish-German	2					2
Italian-German	1					1
Polish-Hungarian	1		1			2
Polish-Lithuanian	2					2
Russian-Lithuanian	1					1
Scotch-Irish	4					4
Austrian-Hungarian		1				1
German-American					1	1
German-Hungarian		1				1
German-Polish		1	1			2
Russian-German		1				1
Irish-Hungarian			1			1
French-American			1			1
Irish-American				1		1
						233

and 15 years, the height of onset (of rheumatic heart disease) being between the seventh and eighth years."

The nationality of the families of the students was as varied as would be expected in a city like Chicago. Americans made up the largest group, and Russians, Italians, and Poles followed in that order (Table IV). No racial or national group has ever been found to be resistant to either rheumatic or congenital heart disease.[9, 10] Only seven of our patients were Negroes, but this was due to the location of the school in the city, and not to a resistance on the part of that race.

Most of the families had four or five children, although one fairly large group of those who died after leaving school were from families with six or more children. The families were rated by the nurse when she made her home calls as either good, fair, or poor from a socioeconomic point of view. Thirty-eight per cent were rated good; 39 per cent, fair; and 23 per cent, poor. These groupings must be compared to the ratings of a public school group in a big city, and not to the population at large, for rheumatic fever is known to be one hundred times more common in the poorer socioeconomic strata. Rheumatic fever and rheumatic heart disease are rarely found in private schools.[10] Also, the Spalding School is located in an exceedingly "poor"[9] neighborhood, and the best of its families are in the lower income brackets.

Our patients were approximately equally divided as to sex, and no difference in severity of the heart disease in either sex was noted.

The grade placement of children with heart disease is affected by their condition only insofar as it keeps them out of school for long periods of time. Otherwise, our students were in the grade in school which was commensurate with their age and mentality, as is the well child. The school itself is able to meet the educational requirements of a standard Illinois elementary and high school.

Thirty-five of these students had been given a psychiatric interview.[*] Seventeen of these are living, and eighteen died after leaving school. Two-thirds of the group appeared to recognize their handicap and to accept it for the most part. Their acceptance had a definite correlation with their identification with the school and their enhanced feeling of security while in school. Some of those who felt or showed this increased security stated that it was because they were one of a group, and not one person singled out for special emphasis because of heart disease. Also, many said they knew being at the school would help their condition, and so eagerly accepted it. Lyon, et al.,[12] whose group of twenty-two children with heart disease were attending regular school, found that many of the special problems of these children, such as worry over, or resentment against, his illness, concealment of it in order to increase his activity, etc., were removed by "conferences with school teachers and school principals, by advice to parents and other children in the family and by the provision of special activity and vocational

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[*] Conducted by Dr. Paul Schroeder and associates at the Institute for Juvenile Research in Chicago.

training for the patients." In general, the interviews led us to agree with Silver:[13] "That the presence of these handicaps has not caused any marked deviations from the standards of ordinary conduct or any disturbance in the development of normal social relationships."

The average length of stay in Spalding School was 2.4 years, although some students attended other special schools in the city before or after Spalding School, and so presumably were in a special school longer. Many patients, if improved while in Spalding School, are labeled "no further special school care felt to be necessary" by their own physician or the Chicago Heart Association school physician. Various other reasons for leaving Spalding School are shown in Table V. It is interesting that only seven out of 233 left against medical advice, which means that no possible excuse for considering them improved enough to be classified in the first group could be found. Three of the seven later died. Only nine out of a total of 109 considered improved enough to leave were in the died-since-leaving-school group. It should be further noted that 19 out of 26 who left school because of the severity of their illness later died.

TABLE V

REASONS FOR LEAVING SPALDING SCHOOL

REASON FOR LEAVING	CASES WITH FULLY COMPLETED RECORDS	DIED SINCE LEAVING SCHOOL	OUT OF TOWN	UNABLE TO LOCATE	NO CO-OPERATION	TOTAL
No further special care felt necessary	76	9	11	12	1	109
Graduated, high school	15	10			1	26
Moved	5	5	6	3	1	20
Working	12	5	2	1	2	22
Overage (staying at home)	9	4	1	1	1	16
Ill at home	3	15	1	1		20
Ill, hospitalized	2	4				6
To parochial school	2			1		3
Left against medical advice	3	3			1	7
Transferred—distance to special school too great	1	1				2
Dismissed to Municipal Tuberculosis Sanitarium (pulmonary tuberculosis)	1					1
Dismissed—pregnant	1					1
						233

The cardiac diagnosis and classification on leaving the school remained the same as that made on entrance in most instances. A few children were thought to have developed further valvular damage, but, in the great majority, clinical observation showed no progression of disease. Occasionally, variations in the clinical signs in cases of congenital heart disease would change the anatomic diagnosis, but it is known that the clinical signs in congenital heart disease are often in-

constant, and therefore this does not imply that the patient's condition is worse.

As previously stated, 130 patients were interviewed and examined to ascertain what had happened to them since leaving the school. The youngest was 17 years old, and the oldest, 33, at the time of the recheck physical examination. There were 65 males and 65 females. Thirty-two of the women were married: fourteen had borne one child; three had two children; one had three children; two had had four pregnancies; three were pregnant. None reported that her heart condition had adversely influenced her pregnancy or labor to any great extent. All of these women stated that the medical care given them during their pregnancies and labors took into account their heart condition. Martin[14] reports similar observations. Stroud and Twaddle[15] reported that one out of 27 had congestive failure at the time of delivery.

One hundred nineteen (60 males, 59 females) reported that they either saw a physician regularly or had been examined at least within the previous three years. Seven (2 males, 5 females) had not seen a physician within three years, but had done so prior to that time. Four (3 males, 1 female) had had no medical care since leaving school. Presumably the effort made in school to educate them to the necessity of frequent medical checkups had some effect. It should be further noted that there were few intervening illnesses, operations, or accidents which required medical attention, other than that necessitated by their cardiac condition.

Twenty-six (20 per cent) had recurrences of rheumatic fever: 13 had one recurrence, 10 had two, one had three, one had five, and one had ten (the latter patient, incidentally, is now quite well and in cardiac classification IIA). Wilson[16] states that the number of recurrences of rheumatic fever tends to decrease after puberty. According to Cohn and Lingg,[17] there is "diminished susceptibility to rheumatic infection at puberty." Therefore, this low percentage of recurrences was to be expected, for most of these students were approaching puberty, or were beyond it, when they left school.

The diagnoses, on the whole, remained the same as those made on leaving school. Because of the lapse of time since the initial infection, it was possible to discard a diagnosis of "potential" or "possible" heart disease for a definite diagnosis of "no cardiac disease." In five cases "auricular fibrillation" had to be added to the diagnosis, and one patient had had auricular fibrillation for two years, but not at the time of the recheck examination. This patient had had five recurrent attacks of rheumatic fever. Of the other patients who had auricular fibrillation, three had had two recurrent attacks of rheumatic fever and two had had one recurrent attack each. Four were classified in Class III and two in Class IIB. Table VI lists fourteen cases of auricular fibrillation, with the number of years during which it is definitely known to have been present. Four cases are from this study. Ten

TABLE VI

CASES OF AURICULAR FIBRILLATION

NUM-BER	CODE NUM-BER	SEX	AGE AT RECHECK EXAMINA-TION	ENTRANCE DIAGNOSIS	KNOWN DURATION OF FIBRIL-LATION (YR.)	COMMENT
1		F	20	Rh. M. I. and S.	4	Completed high school in 4 years without remission of fibrillation
2	17*	F	19	Rh. M. I. and S.	1	
3		F	19	Rh. M. I. and S.	4	Completed high school in 4 years
4		M	22	Rh. M. I. and S. A. I. and S.	1	Completed high school in 5 years with fibrillation during last year
5		M	16	Rh. M. I. and S.	4	
6	13*	F	21	Rh. M. I. and S. A. I. and S.	2	Five recurrent attacks of rheumatic fever
7	161*	M	26	Rh. M. I. and S.	8 mo.	Two recurrent attacks of rheumatic fever
8	27*	F	24	Rh. M. I. and S.	4	One recurrent attack of rheumatic fever
9		F	21	Rh. M. I. and S.	4	
10		M	*Age at Death* 19	Rh. M. I. and S. A. I. and S.	2½	Fibrillated continuously last 2½ years of high school. Completed high school in 4 years. President of his class
11		M	24	Rh. M. I. and S. following scarlet fever	3	Completed high school in 4 years without remission of fibrillation
12		M	18	Rh. M. I. and S.	6	Four years high school with demise 2 months before graduation. Ranked first in his class. Worked after school last 2 years
13		F	17	Rh. M. I. and S.	1	
14		M	15	Rh. M. I. and S.	1	

*Refers to case number in Table I.

others—students at Spalding School, but outside the scope of this study—are included because of interest in the clinical condition and general picture of children who have auricular fibrillation over a long period of time, rather than as a terminal event. Nine (3 males, 6 females) are living. The youngest was 16, the oldest, 26, years of age. The duration of auricular fibrillation varied from eight months to four years; four of these patients have had it for four years. Five (4 males, 1 female) of them are dead. The youngest was 15, the oldest, 24, years of age. Two had had auricular fibrillation one year before death, one, two and one-half years, one, three years, and one, six years, so that

their period of fibrillation could hardly be considered a terminal event. The great majority of them knew when they had auricular fibrillation, but did not exhibit any undue concern over their heart condition. In general, they did well in school.

It is interesting to compare the cardiac classification on recheck examination with that on leaving school. The number of years since these students left the school varies from one to 18 years. Of the 76 who left school because they were considered well enough to attend regular school (see Table V), 24 (6, IIB; 15, IIA; 3, I) are better, 36 (5, F or E; 8, I; 18, IIA; 5, IIB) are the same, 16 (2,F; 3, I; 9, IIA; 2, IIB) are worse, and 2, classed as IIB, are now Class III.

Of the 15 who left because they had completed high school, 6 (1, E; 2, IIA; 3, IIB) are better, 6 (3, IIA; 3, 11B) are the same, 3 (2, IIA; 1, IIB) are worse, and the last-mentioned IIB is in Class III. Of the 5 who moved out of the district, 3 (1, IIA; 2, IIB) are better, one IIB is the same, and one IIA became a Class III.

Of those who left to go to work, 6 (2, IIA; 4, IIB) are better, 5 (1, I; 3, IIA; 1, IIB) are the same, and one IIA became IIB. Of those who stayed at home, 2 in Class IIA are better, 5 (3, IIA; 2, IIB) are the same, 2 (1, I; 1, IIB) are worse, and the last-mentioned IIB is in Class III. Of those too ill to attend school, 2 (1, IIA; 1, IIB) are the same, and one in Class IIA is now in Class IIB.

Of those hospitalized, two in Class IIB are better. Two in Class IIA left to go to parochial school, and are now in Class IIB. Three left against medical advice: two in Class IIB are better, and one in Class IIA is the same. One in Class IIB who lived too far away to continue at the school is now in Class I. One in Class IIB with active pulmonary tuberculosis is now in Class IIA, but is a schizophrenic. One in Class IIA who left because of her pregnancy is now in Class I. To summarize: 48 are better, 56 remained the same, and 26 are worse. Of the five in Class III, all have auricular fibrillation.

It is interesting to note what these persons are able to do. Almost all of them are working. The jobs held cover a wide field:

Commercial art work:
    Poster artist
    Greeting card artist
    Plaster art worker
    Sign painter
Dental technician
Librarian
Photographer
Photographer's model
Piano teacher
Reporter (newspaper)
Soldier (U. S. Army)
Student
Office work:
    File clerk

Window decorator
Factory:
    Candy packer
    Package wrapper
    Packer
    Punch press operator
    Receiving room (clerk)
    Shipping clerk
Barber
Butcher
Carpenter's helper
Electrician's helper
Machinist helper
Plasterer's helper
Plumber's helper

Stenographer
Switchboard operator
Typist
Retail business:
  Purchasing agent
  Order filler
  Shoe store owner
Cashier
Clerk:
  Department store
  Bakery
  Grocery
Dressmaker
Solicitor (outside work)
Theatre usher
"26" girl

Printer's helper
Tool die maker
Cab driver
Car washer
Coal man
Delivery and errand:
  Pharmacy
  Florist
  Stock broker
Domestic:
  Hotel
  Private family
Repair man (hardware store)
Subway mucker
Truck driver
Waiter
Waitress

Only five had never worked or were not working at the time of this study. Many were doing heavy work. Fifty per cent of the women were doing their own housework and taking care of their children as well, and let no one say this is not heavy labor. One man had been accepted by the Army and was in active service. One traveling salesman carried his heavy sample suitcases all day, and climbed many flights of stairs with them.

Their recreational activities cover just as wide a field as did their jobs:

Home
Art work:
  Charcoal drawing
  Water coloring
  Clay modeling
Beauty culture
Cards
Cooking
Crocheting
Knitting
Mechanics
Printing
Photography
Philately
Radio
Reading
Sewing
Music:
  Accordion
  Clarinet
  Piano
  Violin
  Singing
Community activities:
  Boy Scouts
  Girl Scouts

Church socials
Clubs
Dances
Movies
National Guard
Out of doors and sports:
  Baseball
  Basketball
  Bathing
  Bicycling
  Bowling
  Fishing
  Football
  Golf
  Gymnastics
  Hiking
  Horseback riding
  Hunting
  Automobile rides
  Roller skating
  Skiing
  Speed boating
  Swimming
  Tennis
  Travel

These are recreations common to all young people, and the cardiac condition seems to have exerted little influence except insofar as the person was actually limited to sedentary activity. Dancing was a favorite of many, and can scarcely be considered sedentary.

We have been unable to locate 19 of the students. Seven refused to come for examination or to answer any questions, and 21 were reported to be living out of town. However, these latter groups should be considered among the living. Fifty-six are known to be dead, making a mortality of 26 per cent for the entire group. Stroud and Twaddle[15] reported 21 per cent mortality in their series, and quoted Jones's report of 24.2 per cent mortality in his series and Halsey's report on Irvington House patients as 24 per cent. Martin[14] reports 29.9 per cent mortality in his group. However, it must be noted that ten of the 56 who died had congenital heart disease—a total of 18 per cent. Of the group of 158 known to be alive, only 12, or 7.6 per cent, had congenital heart disease. Hedley[18] states that most observers consider "approximately 10 per cent" of deaths from heart disease among young persons to be of congenital origin. Our figure of 18 per cent is higher because this was a selected group of children with severe heart disease who were well enough to attempt some school activity. Children of school age with severe congenital heart disease are more likely to be sent to a school of this kind, if it is at all possible, than children with severe rheumatic heart disease.

The length of time these children lived after leaving the school varied from one to eleven years. Of 9 who left because no further special school care was considered necessary (see Table V), 2 lived eleven years, 1 lived nine years, 1 lived eight years, 1 lived six years, 1 lived four years, 1 lived three years, 1 lived two years, and 1 lived one year. But of those 19 who left because they were too ill to remain in school, 1 lived eleven years, 1 lived nine years, 1 lived five years, 1 lived three years, 5 lived two years, and 10 lived one year or less. Three left against our advice—2 of them had congenital heart disease. One lived two years, 1 lived four years, and 1 lived three years after leaving school. It is interesting that 41 out of this group of 56 had done no work of any kind—even light housework—since leaving school. Considering their economic level and the fact that all the others mentioned some job, however small, it is presumable that these 41 were too ill to work.

We were able to obtain forty-three death certificate reports. Twenty-four definitely stated or clearly implied that the "cause of death" (or one of the contributing factors) was rheumatic heart disease. In eleven cases in which the same diagnosis had been made during life, the "cause of death" was "chronic myocarditis" or an equally nonspecific diagnosis. In eight cases the ante-mortem diagnosis was congenital heart disease. According to the death certificates, two of these patients had died of rheumatic heart disease, one of chronic myocarditis, one of bacterial endocarditis with congenital heart disease as a contributing

factor, one of malignant endocarditis (with no mention of the congenital deformity, even though an autopsy was performed), one of streptococcic meningitis with congenital heart disease a contributing factor, one of morbus caeruleus and patent foramen ovale, and one of cerebral embolism and endocarditis. Two patients died of cerebral embolism. One of them had subacute bacterial endocarditis, and both conditions were found at autopsy; the other had a diagnosis, before death, of congenital heart disease with superimposed rheumatic heart disease. There were three who died of subacute bacterial endocarditis; all three had had rheumatic heart disease. One patient died of lobar pneumonia; his rheumatic heart disease was not mentioned on the certificate. Only four autopsies had been performed; two confirmed diagnoses of rheumatic heart disease; one, previously mentioned, confirmed the diagnosis of cerebral embolus and subacute endocarditis; one, also previously mentioned, was reported as confirming the diagnosis of the cause of death as malignant endocarditis, without any mention of the congenital deformity that was known to have been present.

COMMENT

This is a survey of a group of children with heart disease whose medical treatment was supplemented by their attendance at a special school. Evidence is here presented that these children progressed favorably from the clinical point of view. In addition, they lived at home and continued their education in a normal manner. They and their families received continual intensive advice and guidance through the normal ordinary channels of parent-teacher-school relationship. It should be further noted that patients with congenital heart disease with marked cyanosis—usually severely handicapped—were also enabled to attend school without embarrassment or risk. Authorities[2, 14, 15] agree that patients who have had rheumatic fever need a 'long convalescence, either to prevent the development of heart disease or to treat the heart disease which has already appeared, and that this is best done in a convalescent home. In his survey of facilities available for the care of cardiac children, Hedley[19] discusses types of convalescent institutions in detail, and states that treatment should be planned for "about one year." Of the twelve states who had cardiac programs in operation by January, 1942, eleven had made provision for sanitarium care, and most of them had also provided some plan of foster home care.[20]

A typical state program, as outlined by Galvin,[21] attempts to provide treatment for the sick child and follow-up care for the convalescent child, but it makes no provision for control of the child over a long period of time. However, Galvin[21] states: "information regarding the school child is sent promptly to the school principal and school nurse to protect him not only from undue exposure to colds and unwise activities but also from oversolicitude." In a special school, the child remains in his own home, yet receives such protected schooling. Also, both he and his parents are educated to the special needs of heart dis-

ease in childhood and in the future. Much parental anxiety is removed, and this tends to relieve the cardiac child of one of his greatest handicaps—the oversolicitous and fearful parent.[13, 22]

Utter[23] stresses the need of informing the child about his own care and the avoidance of future infection. Siegel[24] states that children with congenital heart disease whose lesions, although severe, are compatible with a life of limited activity should have "regulation of exercise, anticipation and prevention of intercurrent disease and education for a suitable vocation." White[25] and his group conclude that the child's cooperation is best when the environment is made as homelike as possible. Martin[14] mentions the importance of avoiding wrong diagnoses in order to prevent cardiac neuroses. Also, he stresses the avoidance of partial invalidism among those with heart disease who are able to lead normal, if limited, lives.

In general, authorities are agreed on the need for care of children with rheumatic heart disease long after the initial infection. Convalescent homes are best for that desirable "continuity of care"[26] immediately after the initial illness or the recurrence. But, for long periods thereafter, patients with inactive rheumatic heart disease and children with congenital heart disease need limited activity, medical supervision, and guidance and education for the future. Obviously, as Galvin[27] points out, only limited numbers of patients can be cared for in institutions and foster homes. The special school permits shortening of the period of time during which these facilities are required. Special facilities, such as those described for Chicago, in the local public school system offer any cardiac child the opportunity for a school life which is made more normal by the fact that he is enabled to live with his own family in his own home and to attend school as other children do.

SUMMARY

1. The importance of the public health aspect of cardiac disease in children is discussed briefly.

2. A school program for cardiac children is described.

3. Data are presented on a follow-up survey of all students who had attended such a school. This covered approximately a ten-year period. Of the total of 233 students, 158 were living and 56 were dead.

4. Of 130 examined, 104 had either improved or remained in the same cardiac classification since leaving the school. Their current activities are described.

5. A special school for cardiac children serves the following purposes:

a. It can carry on where the convalescent home leaves off, and can continue for much longer periods of time the kind of medical supervision a child with rheumatic heart disease requires.

b. A more normal life for cardiac children of school age with limited capacity for any activity is provided.

c. Contact is made with the parent, as well as the child, and thus

both can be educated in the practical aspects of the type of living suitable for cardiac children and adults.

Dr. Arthur F. Abt, formerly chief Chicago Heart Association physician at the Spalding School, and now on military leave of absence, initiated this study and has given much of his time and advice to its execution.

We wish to thank Dr. Isaac A. Abt, Miss Elizabeth Stern, and Miss Grace Bennett for their assistance.

The school records were made available to us by the Board of Education of the City of Chicago.

Death certificates were made available to us by the Bureau of Vital Statistics, Cook County Clerk's Office, City of Chicago.

School nurses stationed at the Spalding School by the Board of Health of the City of Chicago assisted in the recheck physical examinations.

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Clinical Reports

ELECTROCARDIOGRAPHIC CHANGES SIMULATING THOSE OF ACUTE MYOCARDIAL INFARCTION IN A CASE OF PERFORATED GASTRIC ULCER

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THE differential diagnosis between myocardial infarction and acute surgical lesions of the upper abdomen is at times difficult, yet obviously of the greatest importance, for the former demands conservative management, whereas the latter may require immediate surgical intervention.

The fairly characteristic electrocardiographic patterns which occur with myocardial infarction make the electrocardiogram a valuable adjunct in the differentiation of these two types of acute disease. However, to interpret properly the electrocardiographic data obtained under these circumstances, certain pitfalls must be avoided, one of which is the not infrequent absence of electrocardiographic changes early in myocardial infarction. Second, one must bear in mind the occurrence of single or multiple coronary artery occlusions in elderly patients in shock,[1] a situation in which myocardial infarction occurs in association with, and probably as an indirect result of, the acute surgical or "shocking" disease. The case described here represents still another pitfall in diagnosis, namely, electrocardiographic changes suggesting acute myocardial infarction without coronary artery occlusion, but in the presence of a ruptured abdominal viscus with associated shock.

REPORT OF CASE

H. V., a white man, aged 68 years, was admitted to the Hospital of the University of Pennsylvania Feb. 8, 1943. On the day of admission, while en route to the Gastrointestinal Clinic, he became weak, collapsed on the street, and was brought into the Hospital by the police. His history was one of upper abdominal pain for the preceding ten years. The pain was dull, nonradiating, occurred usually ten to fifteen minutes after meals and during the night, and was relieved by alkali. During the two months prior to admission, he had lost about 40 pounds in weight, probably because of marked anorexia. During this time he also had melena, hematemesis, and mental confusion, and had resorted to the use of sodium bicarbonate every few hours. There was no history of exertional dyspnea or angina of effort.

Physical examination on admission revealed an emaciated white man who appeared anemic, dehydrated, and chronically ill. The tempera-

ture was 98° F., the pulse rate, 78, and the blood pressure, 170/100. The chest was emphysematous. The heart did not seem enlarged on clinical examination. The first heart sound was distant, the aortic second sound was accentuated, and a soft blowing systolic murmur was heard at the apex. Examination of the abdomen revealed moderate distention and slight bilateral upper abdominal tenderness without rigidity. The edge of the liver was felt 2 cm. below the right costal margin, and was not tender. Deep palpation just below the liver margin revealed a somewhat tender, round, ill-defined mass, apparently about 6 cm. in diameter, which did not move on respiration. The peristaltic sounds were of normal frequency and pitch. Rectal examination was noncontributory. Examination of the extremities revealed obvious and marked peripheral arteriosclerosis. The tentative diagnosis on admission was chronic peptic ulcer, probably with malignant change.

Laboratory studies disclosed an erythrocyte count of 4,200,000, a hemoglobin of 11 Gm. (75 per cent), and a leucocyte count of 9,400. The neutrophiles were 66 per cent, the lymphocytes, 24 per cent, the monocytes, 9 per cent, and the eosinophiles, 1 per cent. Urinalysis showed a specific gravity of 1.022, 1 plus albumin, no sugar, and only an occasional leucocyte per high-power field. The serum CO_2 was 94 volumes per cent, the serum chloride, 83.9 meq. per liter, and the serum proteins, 6 Gm. per 100 milliliters.

The patient was allowed nothing by mouth, and an intravenous infusion of 5 per cent glucose in .85 per cent sodium chloride solution was given. By the morning of Feb. 9, 1943, he was feeling much improved. His temperature was 98.3° F. The hemoglobin had fallen to 48 per cent and the leucocyte count to 6,000, probably as a result of better hydration. Frequent bland feedings were begun.

At noon on Feb. 10, 1943, the patient suddenly developed severe epigastric pain, with tenderness and rigidity of the entire abdomen and absence of peristalsis. The blood pressure fell to 60/30, the pulse rate rose to 125, and the patient appeared to be in extreme shock. A diagnosis of ruptured peptic ulcer was made, with which a surgical consultant agreed. However, an electrocardiogram taken at this time (Fig. 1) revealed S-T segment depression in Leads I, II, CR_4, and CR_5, strongly suggesting infarction of the lateral wall of the left ventricle. Nevertheless, in spite of this, the history and physical examination seemed to point clearly toward an abdominal catastrophe, perhaps associated with acute myocardial infarction. The surgical consultant felt that the almost moribund condition of the patient contraindicated immediate operation, and the usual measures to combat shock were taken. The temperature rose to 101° F. (rectal), the blood pressure remained quite low, the pulse became imperceptible, and the patient died seven hours after the onset of the collapse.

NECROPSY

The necropsy, performed by Dr. Melvin Friedman on Feb. 11, 1943, revealed the following: There was generalized peritonitis, and culture of the peritoneal exudate showed nonhemolytic streptococci, *Streptococcus fecalis*, and *Bacillus coli*. The lungs were congested. The spleen and kidneys showed moderate arteriolarsclerosis. The pancreas, liver, gall bladder, adrenals, and prostate were normal. There was an extensive ulcer crater about 6 cm. in diameter and 1 cm. in depth in the prepyloric region of the stomach on the lesser curvature. On the anterior side of the ulcer there was a 1 cm. perforation. Microscopic examination revealed no evidence of malignant change. The heart, which
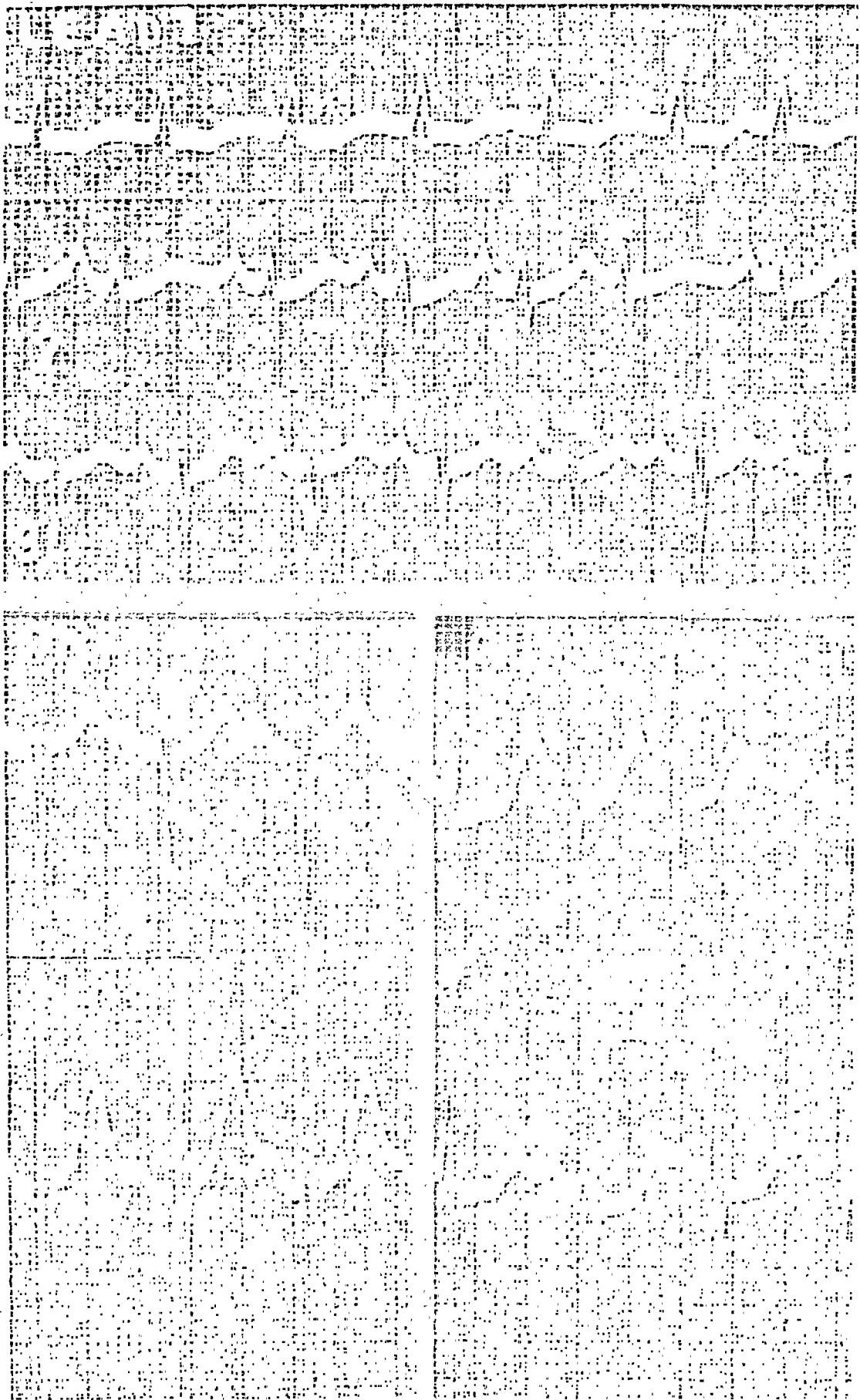
Fig. 1.

weighed 430 grams, was examined with the greatest care by Dr. Friedman and one of us (F.D.M.). The coronary vessels were followed out to their smallest radicles. The arteries were quite sclerotic, particularly the circumflex branch of the left coronary. However, no fresh or old occlusions could be demonstrated. The heart was next hardened in formalin for several days, then cross-sectioned in slices 1 cm. thick from apex to base. In scattered areas of the myocardium, with no distinct anatomic distribution, there were a few tiny spots of fibrosis. Histologic study of multiple areas of the myocardium, particularly the lateral wall of the left ventricle, revealed no abnormalities except occasional small areas of old fibrosis.

DISCUSSION

That abdominal lesions may simulate coronary occlusion closely has been clearly recognized, and the diagnostic difficulties resulting therefrom are well illustrated, for example, by the reports of Barker, et al.,[2] and Averbuck.[3] The story of the acute attack and the physical examination alone may be confusing, but, when accompanied by a long-standing history of mild to severe cardiac distress, the diagnostic problem often becomes highly perplexing. Since the electrocardiogram would appear to be a logical aid in differential diagnosis, it becomes important then to recognize its limitations under these conditions.

Fitz-Hugh and Wolferth[4] have demonstrated electrocardiographic changes, mainly flat or inverted T waves in Leads I and II, which occurred in the presence of gall bladder disease and disappeared after appropriate surgical intervention. These changes they interpreted as meaning that gall bladder disease in some as yet unexplained fashion affects the myocardium. McGee, et al.,[5] have reported a case of perforated duodenal ulcer with small but definite S-T segment elevation in Leads II, III, and a chest lead, as well as T-wave inversion in Leads II and III. This patient had a history of exertional epigastric pain, making the diagnosis yet more difficult. Necropsy showed little evidence of coronary artery disease. These authors felt that insufficient oxygenation of the myocardium resulting from the low blood pressure of shock was the probable explanation of the electrocardiographic changes. Gottesman, et al.,[6] have reported a case of acute pancreatitis with depressed S-T segment in Leads II and III and a chest lead, and diphasic T waves in Leads I, II, and III, and a chest lead. Upon recovery, the patient had a quite normal electrocardiogram.

In addition to this electrocardiographic mimicry of myocardial infarction, one must also recognize the possibility of the actual coexistence of abdominal disease and coronary occlusion. Blumgart, et al.,[7] have emphasized the occurrence of multiple coronary artery thrombi in patients with antecedent shock. The majority of their patients were elderly, were known to have had pre-existing heart disease, and at necropsy showed evidence of coronary artery disease. No electrocardiographic data were given, however.

The explanation for the abnormal electrocardiographic patterns in our case can be only speculative. Unfortunately, no previous electrocardio-

grams had been taken. Actual arterial occlusion seems to have been ruled out by careful post-mortem study. The theory that the changes were "reflex" in origin would seem to have little clinical or experimental evidence in its favor. Since the systemic blood pressure at the time the electrocardiogram was taken had fallen to 60/30, and the coronary arteries were shown to have greatly narrowed lumina, it would seem more logical to attribute the abnormal patterns to impaired blood supply to the myocardium, with resultant poor oxygenation of the muscle. In fact, the electrocardiographic changes in this case are quite similar to those which occur during an anginal attack or during the breathing of an oxygen-poor mixture. It seems clear, therefore, that, in a case of coronary arteriosclerosis, the possibility exists that any disease causing shock may give rise to electrocardiographic patterns of the "anoxemic" type, which, since they are so much like those seen in lateral wall infarction, may lead to an erroneous diagnosis of coronary occlusion. This likelihood of error in diagnosis becomes still greater when the clinical observations are equivocal, a situation often present with acute surgical lesions of the upper abdomen.

SUMMARY

A report is presented of a case of perforated gastric ulcer, with shock, in which an electrocardiogram strongly suggested infarction of the lateral wall of the left ventricle. Careful post-mortem study of the heart revealed arteriosclerotic narrowing of the coronary vessels, but no evidence of actual occlusion or of myocardial infarction.

The presence of marked coronary artery narrowing and the fact that the blood pressure was greatly lowered have led us to postulate insufficient blood supply to the myocardium and, therefore, anoxemia of the muscle as the cause of the electrocardiographic abnormalities.

It is emphasized that the electrocardiogram can play an important role in the differential diagnosis between coronary artery occlusion and acute abdominal lesions, but that it may be confusing and actually misleading unless one recognizes its limitations and possible mimicry under these conditions, particularly when shock is present.

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Abstracts and Reviews

Selected Abstracts

Nickerson, J. L., and Curtis, H. J.: *The Design of the Ballistocardiograph.* Am. J. Physiol. 142: 1, 1944.

An experimental and theoretical study of the human ballistocardiograph has been undertaken with a view to designing an apparatus which will measure accurately and easily the motion of the body which occurs as a result of the heartbeat. Both approaches to the problem have demonstrated that:

It is absolutely necessary to have the bed damped by a device which introduces no friction. Since both over and under damping yield errors which are difficult to evaluate, the damping should be critical for the total load.

The restoring force on the bed is most easily specified by the undamped frequency of oscillation of the loaded bed. True ballistic records are obtained only when frequencies somewhat less than 1 per second are used. When higher frequencies are used, the errors in amplitude and wave form increase with the frequency.

Measurements at very low frequencies are difficult to make. However, at frequencies between 1 and 1.5 per second, the difficulties are reduced somewhat and the errors are not serious.

It was found that at frequencies above 2 per second the subject and the bed do not move in unison, and the pattern recorded depends in part on the elastic properties of the tissues of the subject. This leads to serious errors at high frequencies.

Complete specifications are given for the construction of the bed used in this work.

AUTHORS.

Gregg, D. E., and Shipley, R. E.: *Augmentation of Left Coronary Inflow With Elevation of Left Ventricular Pressure and Observations on the Mechanism for Increased Coronary Inflow With Increased Cardiac Lead.* Am. J. Physiol. 142: 44, 1944.

Left coronary inflow is found to increase significantly in the anesthetized open-chest dog, when the load upon the left ventricle is increased by constriction of the aorta (central to the coronary orifices). This flow response is similar to that obtained previously in the right coronary artery in the presence of pulmonary artery constriction.

Measurement of cardiac input and oxygen consumption in the presence of an augmented load on either right or left ventricle has demonstrated an increase in the work and metabolism of the respective ventricle. In consideration of the increased coronary inflow observed, the two ventricles have at their disposal a compensatory means by which their blood supply can, at least in part, be adjusted to their work and metabolic requirements. It is suggested that the coronary dilatation arises from an increased local production of metabolites and/or the creation of local relative anoxia due to increased O_2 utilization.

If the experiments are intentionally prolonged (for several hours) and the coronary artery is perfused at constant pressure, the coronary flow response ultimately becomes a sustained decrease. As observed under these conditions, and by

others using heart-lung and isolated heart preparations, the decrease in coronary inflow is regarded as an "abnormal" response to an increased cardiac load.

AUTHORS.

Saracoglu, K.: A Rare Case of Complete Heart Block. Brit. Heart J. 6: 93, 1944.

A case of complete heart block with a rare degree of auricular bradycardia is described. The ventricular rate was 40 and the auricular rate 30 a minute.

As the auricular rate was not influenced by atropine or adrenalin it was thought to be due to coronary disease and not to increased vagal tone.

AUTHOR.

Neubauer, C. Heart-Block in Diphtheria. Brit. J. Child. Dis. 40: 93, 1943.

The author describes a series of forty-four cases of heart block in children suffering from diphtheria, observed from the onset to either convalescence or death. Of the cases described, thirty presented a partial, and fourteen a complete, heart block.

The various clinical signs are described, and an abbreviated report for each case is given.

McCulloch.

Logue, R. B., and Hanson, J. F.: Heart Block. A Study of 100 Cases With Prolonged P-R Interval. Am. J. M. Sc. 207: 765, 1944.

A series of 100 cases of heart block with prolonged P-R intervals is reported. The study consists of a review of 6,732 electrocardiograms taken on 4,264 patients at the Lawson General Hospital. The etiological classification of block is given with a discussion of causative factors. The P-R intervals of the 100 cases are tabulated, as well as variations in age and pulse rates. The normal range of the P-R interval is discussed. The belief is expressed that an occasional person may have a prolonged conduction time which is normal for that person and is perhaps associated with an individual variation of vagal tone. Observations are given regarding the effects of atropine in heart block with an expression of the authors' beliefs, as well as those of other observers, concerning its use.

AUTHORS

Scherf, D., and Klotz, S. D.: Electrocardiographic Changes After Acute Loss of Blood. Ann. Int. Med. 20: 438, 1944.

Fifteen cases of profuse gastric hemorrhage are reported. All but one showed alterations of the T wave, and some of the S-T segment as well, if electrocardiograms were taken soon after the hemorrhage, and daily thereafter. Of three cases of hemorrhage from other sources, two presented similar electrocardiographic alterations.

The first change to appear was lowering of the T waves. More advanced alterations consisted of disappearance or inversion of these waves and depression of the S-T segment. Slightly lowered voltage of the QRS complex was occasionally observed.

The changes in the electrocardiogram vanished in two to nine days; they developed in the absence of shock and without severe anemia and were independent of the hemoglobin level.

The effect of phlebotomy on the electrocardiogram was studied in thirty-three cases. Alterations were observed eight times. Although they may develop after the removal of 450 c.c. of blood, they may not appear with a venesection of 1,000 c.c. The appearance of electrocardiographic changes after an acute blood loss

has particular importance in the differential diagnosis between internal hemorrhage with cardiac symptoms and the cardiac manifestations associated with coronary thrombosis and pulmonary embolism.

AUTHORS.

Gross, R. E.: Complete Surgical Division of the Patent Ductus Arteriosus. Surg., Gynec. & Obst. 78: 36, 1944.

Ligation of a patent ductus arteriosus has produced satisfactory closure in most of the fourteen cases in which it was used as the only method of obliterating the shunt. Better results were obtained in another series of twenty-eight patients in whom the ductus was ligated and was also wrapped with cellophane to promote regional fibrosis. While this latter method has been an improvement over the earlier procedure, it has failed in a few instances to produce absolute stoppage of the fistula. A new technique is now presented for complete division of the ductus which insures prompt and complete closure of this vessel. It has been performed in fourteen patients, two of whom had a superimposed *Streptococcus viridans* and endocarditis. All the patients have recovered, and none has had any important complication from the operative undertaking.

AUTHOR.

Weber, M. L.: Perforation of the Interventricular Septum Following Infarction; Intravitam Diagnosis. Ann. Int. Med. 19: 973, 1943.

A modern review of the literature and an additional case of perforated septum following cardiac infarction, diagnosed before death, are presented. Comments on the clinicopathologic syndrome are made.

AUTHOR.

Sodeman, W. A.: The Systolic Murmur. Am. J. M. Sc. 208: 106, 1944.

Interest in the significance of the systolic murmurs is especially important at this time when the question of physical fitness of draftees for military service comes up frequently. The author reviews all the important recent literature and correlates it with the early development of the interpretation of these murmurs in cardiology. The article is of considerable importance, since the need for correct interpretation of this murmur arises frequently in civil life as well.

MCCULLOCH.

Barron, D. H.: The Changes in the Fetal Circulation at Birth. Physiol. Rev. 24: 277, 1944.

A great deal of information has been accumulated in recent years by direct methods of study carried out by Bancroft on the oxygen content of fetal blood, and by Barclay, using radiopaque substances in the blood stream to follow by cinematograph the pattern of circulation and the movement of blood, especially in the fetus delivered by cesarean section. The author reviews these studies, together with those carried out by other workers. He also reviews the recent work explaining the closure of the ductus arteriosus, ductus venosus, and foramen ovale. There is at present no satisfactory explanation of the mechanism initiating the closure of the ductus arteriosus. The available evidence indicates that the ductus arteriosus and the venosus are closed functionally within a few minutes after birth by the action of sphincter muscles appropriately placed. The closure of the foramen ovale may take place abruptly or immediately after birth, but the forces responsible for its closure have not been described.

MCCULLOCH.

Coburn, A. F.: The Prevention of Respiratory Tract Bacterial Infections. J. A. M. A. 126: 88, 1944.

The United States Navy is engaged in a long-term program for the control of streptococcic infections and their disabling sequelae. One component of this program involves mass prophylaxis with sulfadiazine. Prophylactic doses of this drug were given continuously to about 250,000 naval trainees between December, 1943 and April, 1944. This preliminary report deals with observations on only 30,000 men at three camps.

These observations indicate that the continuous ingestion of 1 Gm. of sulfadiazine daily is adequate (a) to check a well-advanced streptococcic epidemic, (b) to check a streptococcic outbreak at its onset, and (c) to protect 85 per cent of susceptible recruits from implantation with bacterial respiratory pathogens.

These observations also suggest that a continuous daily dose of 0.5 Gm. of sulfadiazine (affording a mean level of 1.4 mg. per 100 c.c. in the blood and perhaps 0.8 mg. per 100 c.c. in secretions of the respiratory tract) is almost 85 per cent effective in preventing implantation by *Streptococcus haemolyticus*.

The only untoward effect of mass sulfadiazine prophylaxis is the occurrence of evanescent rashes in 0.5 per cent and dangerous constitutional disturbances in 0.01 per cent.

Mass sulfadiazine prophylaxis is effective (a) in checking bacterial infections of the respiratory tract, (b) in preventing the development of disabling sequelae caused by these bacteria, and (c) in aiding the economy of a nation at war.

AUTHOR.

Cluxton, H. E., and Krause, L. A. M.: Acute Lupus Erythematosus Disseminatus. Ann. Int. Med. 19: 843, 1943.

Four cases, two colored and two white females, are used to emphasize the clinical aspects and to illustrate the variability of the symptom-complex.

Acute lupus erythematosus disseminatus is a disease of unknown etiology associated with widespread visceral lesions predominantly involving the kidneys, lymph nodes, blood vessels, serous and endocardial surfaces, as well as the skin. There is a marked predilection for females in the second and third decades. The prognosis is grave and the average duration of the disease is approxmiately eighteen months. The clinical picture is variable; however, the skin lesions, leukopenia with secondary anemia, arthritis, prolonged fever, and signs of renal involvement are prominent features that should make the diagnosis possible. The avoidance of any form of actinic therapy, except perhaps the roentgen irradiation of the ovaries, and the danger of eradication of foci of infection during the acute phase cannot be overemphasized.

AUTHORS.

Lambeth, S. S.: Peripheral Circulatory Collapse in Toxemia of Pregnancy. Am. J. Obst. & Gynec. 47: 402, 1944.

Nine patients with varying degrees of circulatory collapse have been discussed. Whole blood plasma apparently is effective therapy for peripheral circulatory collapse in toxemia of pregnancy if used in the early stages.

AUTHOR.

Mahorner, H.: Control of Pain in Posttraumatic and Other Vascular Disturbances. Ann. Surg. 119: 432, 1944.

Sixty patients, with conditions requiring temporary or permanent interruption of the sympathetic nerves, have been admitted to my private services at Touro

Infirmary and the Baptist Hospital. Twenty-two operations for permanent section of the sympathetic nerves have been done in this group.

Pains influenced by interruption of sympathetic nerve function are varied. They occur in vascular disease with associated vasospasm and may be attributable not only to ischemia, but also directly to the vascular spasm. Vascular changes occur and persist after trauma, and pain associated with these may prolong disability unduly. These pains may be surprisingly relieved by paravertebral sympathetic nerve blocks permitting more active physiotherapy for mobilization of joints. Such repeated nerve blocks may often shorten a convalescence dramatically. Cases are presented which illustrate this.

Sympathectomy is indicated in all patients with thromboangiitis obliterans under the age of 50 years. The operation gives many times more increase in vascular reserve in patients with early Buerger's disease than in those affected with a late stage, for which it is too frequently reserved.

Raynaud's disease is not a fault of the sympathetic nervous system. Sympathectomy for it is frequently disappointing, and eventually may be discarded entirely. These and other phases of the role of the sympathetic nervous system in vascular diseases were discussed.

AUTHOR.

Dauber, D. V.: Spontaneous Arteriosclerosis in Chickens. Arch. Path. 38: 46, 1944.

Spontaneous arteriosclerosis of the aorta develops in 45 per cent of commercial roosters and hens over 1 year of age. The incidence of macroscopic lesions is the same in both sexes. Hens alone show fatty lesions of the intima of the ascending aorta and arch, while both roosters and hens commonly have intimal lesions of the abdominal aorta.

Arteriosclerosis in the chicken resembles human arteriosclerosis. Arteriosclerosis occurring spontaneously resembles that produced by cholesterol feeding.

The chicken is a suitable animal for the experimental production of arteriosclerosis if used before the age of 6 months, when spontaneous arteriosclerosis begins to occur. It is, furthermore, a suitable animal for studies on the prevention of arteriosclerosis because of the high incidence of the spontaneous disease and the early age at which it begins.

AUTHOR.

Pearce, M. B.: Varicose Veins. Surgery 14: 901, 1943.

One hundred forty-one cases of varicose veins are reported. All those involving the long, saphenous were treated by uniform ligation of all its branches and the saphenous itself at the fossa ovalis without injection of sclerosing fluid into the thigh, together with ligation and injection of the internal saphenous at the lower thigh.

It is believed that complete emptying of the veins by compression bandages of the ACE or rubber type is a distinct advantage in reducing the size of the thrombi and insures better diffusion of the sclerosing fluid into the most distal ramifications of the varicosities.

Five cubic centimeters of sodium morrhuate produce excellent thrombosis in varicosities of the lower leg, and this is the maximum amount used in any single vein.

It would appear that this technique yields a complete obliteration of all varicosities without untoward manifestations.

No recurrences have been noted but it is unquestionably too soon to estimate this phase of the subject. It is hoped that a supplementary report may be made in the future.

AUTHOR.

Lauson, H. D., Bradley, S. E., and Cournand, A.:   The Renal Circulation in Shock.
J. Clin. Investigation 23: 381, 1944.

The changes in renal vascular dynamics resulting from peripheral circulatory failure have been investigated by means of the clearance methods in thirty-five human cases.   The study was part of the comprehensive investigation of the circulation in shock carried on at Bellevue Hospital.

The following conclusions may be drawn:

The rate of glomerular filtration and effective plasma flow are reduced in practically every case of shock.   The reduction is variable, but roughly parallels the degree of shock.

In most cases, the decrease is greater than can be accounted for solely on the basis of reduced arterial pressure, suggesting active vasoconstriction in the renal vessels.   The relationship between the renal blood flow and general circulation has been expressed in terms of two calculated values: The renal fraction, which designates the approximate proportion of total blood flow (cardiac output) which circulates through the kidneys, and the effective renal vascular resistance, which indicates the relation between systemic blood pressure and the renal blood flow. The decrease in renal fraction usually observed reveals that a smaller proportion of the cardiac output flows through the kidneys, indicating that blood is shunted away from the kidneys during shock.   The increase in renal resistance indicates that renal vasoconstriction is the mechanism responsible for this redistribution of the circulation.

In general, the lowest clearances were associated with lowest blood pH values, but several lines of evidence indicate that acidosis is not the primary cause of decreased renal circulation.   On the contrary, renal ischemia probably augments the acidosis resulting from widespread tissue anoxia.

Sources of error and limitations inherent in the clearance methods as applied to the study of shock are discussed.   It is concluded that the clearances give a reasonably accurate description of the status of the renal circulation in this condition.

Urine flow is uniformly reduced and, in extreme cases, total anuria occurs. In general, the degree of oliguria reflects the reduction in rate of glomerular filtration, which in turn is related to the reduction in renal blood flow.

From a limited experience, the impression has been gained that acute alcoholism complicating slight or moderate oligemia tends to result in a relatively generalized vasodilatation, which is reflected in the kidney by a lower filtration fraction and a renal blood flow larger than in nonalcoholics with similar levels of blood pressure.

The influence of blood or plasma transfusion upon the clearances has been studied.   There is a tendency for the filtration fraction to increase, suggesting efferent arteriolar constriction.   The filtration rate increases with the rise in arterial pressure, but the renal blood flow tends to remain low or fall to subnormal values after a temporary increase.

In spite of the approximate return to normal of blood pressure and cardiac output, the renal circulation has, in most of the cases which have been adquately studied, failed to improve proportionately during the period of emergency treatment.   However, measurements repeated several weeks later revealed a normal filtration rate and effective renal blood flow in all the cases so studied.

This investigation confirms the hypothesis that the urinary findings in shock, namely, oliguria or anuria, and loss or impairment of concentrating power, are the result of decreased circulation through the kidneys.

Therapy of shock in relation to the kidney is briefly discussed.

<div align="right">AUTHORS.</div>

Blalock, A., and Park, E. A.: The Surgical Treatment of Experimental Coarctation (Atresia) of the Aorta. Ann. Surg. 119: 445, 1944.

These experiments were undertaken with the idea of devising a means for the surgical treatment of coarctation of the aorta. At a one-stage operation the thoracic aorta was divided, the two ends were closed, and the proximal end of the divided left subclavian artery was anastomosed to the side of the aorta beyond the point of its division. Some of the animals survived this procedure, and there was evidence of adequate blood flow to the posterior part of the body. The possible clinical application of these studies is discussed.

AUTHORS.

Cooke, W. T., and Taylor, A. B.: Treatment of Subacute Infective Endocarditis With Heparin and Chemotherapy. Brit. Heart J. 5: 229, 1943.

Five patients were treated with combined chemotherapy and intravenous heparin. All died, and, in one, this was probably due to the heparin therapy.

Twenty patients (including the five treated with heparin) were studied under treatment with sulfonamide derivatives. Five were totally unresponsive; twelve were moderately controlled. Life was prolonged in some, but all eventually died. Three patients became apyrexial; one died after forty-five days of normal temperature, but, as there was no autopsy, neither the diagnosis nor the state of the lesion could be determined. A second died one year after the onset of his infection and eight months after the control of his pyrexia by sulfapyridine; autopsy showed healed lesions of infective endocarditis. The third is well and working at his occupation as a milk-roundsman at the present time, twelve months after his discharge from the hospital.

Intravenous heparin did not prove of value in our cases and, as others have found, should not be used in these cases.

Prolonged chemotherapy offers a chance of cure to a few patients, though the great majority will not be so benefited. The dangers of such prolonged therapy are small and should not weigh against the chances of a successful outcome.

AUTHORS

McMillan, R. L.: Ventricular Tachycardia as a Therapeutic Problem in Coronary Thrombosis. South. M. J. 36: 800, 1943.

Ventricular tachycardia as a complication of severe myocardial disease has been presented from the standpoint of etiology, pathologic physiology, diagnosis, treatment, and prevention. Two cases with successful quinidine therapy have been presented.

AUTHOR.

Governale, S. L., and Rink, A. G.: Spontaneous Renal Apoplexy With Resuscitation After Cardiac Arrest. Brit. M. J. 2: 43, 1944.

A case of spontaneous renal apoplexy due to malignant hypertensive cardiorenal disease has been presented. The patient's heart stopped during operation. Cardiac resuscitation was accomplished by cardiac massage, intracardiac injection of stimulants, and intraventricular infusion of blood and saline. Life was restored for a period of eighteen hours after the operation. Death ensued from secondary or recurrent right renal hemorrhage. Perusal of the literature does not disclose any previously reported case of intracardiac or intraventricular infusion.

AUTHORS.

Book Reviews

HYPERTENSION AND HYPERTENSIVE DISEASE: By William Goldring, M.D., Associate Professor of Medicine, New York University College of Medicine, and Herbert Chasis, M.D., Assistant Professor of Medicine, New York University College of Medicine. The Commonwealth Fund, New York, 1944, 241 pages, 53 illustrations, $3.50.

Throughout this book the authors subscribe to the idiopathic, "functional," non-renal origin of so-called *essential* human hypertension and to the secondary development of the organic vascular disease (intrarenal included) so frequently found associated with this condition. It is a striking and interesting fact, however, that in their enumeration of the abnormal conditions usually associated with true (systolic and diastolic) hypertension, all but three of the eleven conditions mentioned usually involve some type of renal abnormality. Although the authors admit that most of these diseases of the kidney, because they are "primary," may be the initial cause of the hypertension which follows their development, yet they deny that the organic vascular disease of the kidney of essential hypertension is the initial cause of the elevated blood pressure, because they consider, without proof, that the intrarenal vascular disease is secondary to the hypertension. The frequent occurrence of vascular disease (indistinguishable from that observed in essential hypertension) in organs other than the kidney in nonhypertensive individuals, the much more frequent (almost invariable) occurrence of vascular disease in the kidney in cases of essential hypertension, the experimental production of hypertension by a method which involves only a change in renal hemodynamics that reproduces the renal hemodynamic disturbance of human essential hypertension, and, finally, the absence of development of any changes resembling arterio- or arteriolosclerosis in animals with long-standing, benign, experimental, renal hypertension, fail to convince the authors of the possible primary renal origin of human, essential hypertension. Indeed, as an expression of the opposite view, this book is excellent and valuable.

The authors come to the unequivocal conclusion that the origin of essential hypertension is unknown but not renal. They agree that the elevation of the blood pressure is due to increased peripheral vascular resistance, and conclude that the primary mechanism which induces this must be humoral. Although they have shown that the only significant primary changes observed in the earliest cases of human essential hypertension involve functional hemodynamic and excretory alterations of the kidney, they conclude that these changes are due to the spasm of efferent glomerular arterioles and are therefore secondary to the hypertensive process which is initiated by a hypothetical humoral mechanism not of renal origin. They evidently attach little importance to the absence of efferent glomerular arteriolar spasm and of renal hemodynamic and excretory disturbances in types of hypertension that are not of renal origin, such as experimental neurogenic (carotid sinus hypertension), and humoral (pheochromocytoma of the adrenal) human hypertension. In neither of these types of hypertension have afferent glomerular arteriolar constriction, with diminution in effective renal blood flow, reduction of maximum tubular excretory capacity, and increase in glomerular filtration fraction been demonstrated. This means the attribution of a selective reaction to the efferent glomerular arterioles, which is hardly justifiable.

It is not the intention of the reviewer here to discuss the validity of the interpretation of the special measurements of renal hemodynamics and of renal execretory function devised by Homer Smith and used in all the studies referred to in

this book. Suffice it to say that the authors themselves admit that other interpreta-
tions, of at least some of the data, are possible, and that dogmatic statements about
their significance in any estimation of the state of renal excretory function and
hemodynamics are not yet entirely justifiable. Although sophistical and philo-
sophical interpretation of scientific data is not only permissible, but desirable, the
dangers must not be overlooked, and are recognized by these authors.

The material presented in the body of the book and the details given in the
appendix constitute an excellent summary of the important contributions of, and
methods developed by, Homer W. Smith and his various collaborators, among whom
are included the authors of this book. The chapters on the medical and surgical
treatment of hypertension and on the management of hypertensive disease are ex-
cellent critical summaries of these topics and constitute important parts of this
valuable contribution to the literature on hypertension.

<div align="right">HARRY GOLDBLATT.</div>

PATHOLOGY AND THERAPY OF RHEUMATIC FEVER: By Leopold Lichtwitz, M.D., late
   Chief of the Medical Division of Montefiore Hospital and Clinical Professor of
   Medicine at Columbia University, with a foreword by William J. Maloney, M.D.,
   Grune and Stratton, New York, 1944, 225 pages, 69 illustrations, $4.75.

If this small volume were less excellent, it is conceivable that one might wish
to temper criticism because of the untimely death of the author before its publi-
cation. But it stands so firmly on its merits, it contains so many admirable chap-
ters, that there is no occasion for anything other than frank appraisal, so far as
present knowledge and the limitations of reviewers will permit this.

It is perhaps the definitive statement of the theory which holds that allergic
phenomena are the basis of rheumatic fever. Surely it is the most persuasive
and eloquent presentation of this belief that has yet appeared, and it is difficult
to believe that the evidence supporting it could be marshalled with greater skill
or stated more lucidly than the author has done in this, his last work. The trend
of thought in recent years, at least in this country, has been away from this hy-
pothesis, but, until a specific agent has been proved solely responsible for all the
manifestations of rheumatic fever, there will doubtless be many who will continue
to regard allergy as playing some part in its genesis. Let it not be thought that
the author has presented only the European point of view of fifteen years ago;
he has indeed done this with great skill, but he has also considered all recent work
bearing on the pathogenesis and treatment of the disease, including many papers
published within the past two years.

To present the author's views fairly and adequately in his own words would
require extensive quotations, but one can scarcely resist the temptation to extract
a few words from the first two pages, which are devoted to a definition of rheu-
matic fever. "Rheumatic fever is a noninfectious disease. It is not caused by
a specific microorganism or virus, but by a sensitization to antigens, protein in
nature, which in most cases are products of microorganisms. These microorgan-
isms may be either pathogenic or nonpathogenic. . . . Commonly, the sensitization
tends to persist indefinitely, and in this chronic stage it may be either continu-
ously or intermittently evident. When the sensitization rises, the rheumatic mani-
festations increase; when the sensitization falls below the threshold of clinical
activity, the disease has an intermission. Reactivation is brought about not only
by the specific antigen which initiated the disease, but also by a number of non-
specific factors, any one of which will affect the morbidly sensitized defense
mechanism of the patient in a characteristically rheumatic manner. Thus fatigue,
a chill, an adventitious infection, a slight injury, a touch of indigestion, a mental
upset, or increased bodily activity may cause the rheumatic to relapse from a
quiescent into an acute febrile state. . . . The rheumatic attack strikes at tissues

of mesenchymal origin. As these are an integral part of all organs or structures, local lesions may appear in any part of the body. . . . No matter where the rheumatic lesion occurs—whether in the heart, the meninges, or the joints—fundamentally, its nature is the same. It starts with a swelling of the base substance of the connective tissue. This swelling may clear up, or the process may go on to produce degenerative changes.''

There are splendid chapters upon the incidence of rheumatic fever and the influence of personal factors, upon its general pathology and systemic phenomena, and upon rheumatic disease of the heart and the blood vessels. Full and detailed consideration is given to the effects of the disease upon the joints, muscles, skin, nervous system, and various special organs or systems other than the cardiovascular. The longest chapter in the book, and one to be warmly commended to all interested in the clinical aspect of rheumatic fever, is that dealing with therapy. It is comprehensive, detailed, up to date, and informed by sound clinical judgment.

Especially to be commended is the arrangement of the extensive bibliography; every chapter is followed by a long list of appropriate references.

One cannot dismiss this volume without a word of heartfelt praise for the eight-page foreword by Dr. Maloney, which is a masterly summary of the book; a brief, but eminently fair, presentation of the views of the author. The opening page, relating to the discovery of salicylates, is one of the most charming and delightful accounts to be found in recent medical literature. There must be few, indeed, who can read this page and not continue eagerly through those that follow, revealing as they do the warm affection and admiration of Dr. Maloney for the author and for ''this great book.''

H. M. MARVIN.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

Executive Committee.

Original Communications

THE INFLUENCE OF AUTONOMIC IMBALANCE ON THE HUMAN ELECTROCARDIOGRAM

I. UNSTABLE T WAVES IN PRECORDIAL LEADS FROM EMOTIONALLY UNSTABLE PERSONS WITHOUT ORGANIC HEART DISEASE

MAJOR MARTIN H. WENDKOS, M.C.
ARMY OF THE UNITED STATES

INTRODUCTION

THE recent recommendations by the American Heart Association that multiple precordial leads be employed routinely was intended primarily to provide a more exact means of recognizing organic myocardial change.[1] However, my analysis of the electrocardiographic data in a group of soldiers suffering from neurocirculatory asthenia has indicated that, even when the subject is recumbent, and in the absence of genuine heart disease, bizarre T waves which are indistinguishable from those produced by structural changes can occur in chest leads derived from one or more of the several accepted positions to the left of the sternum. A similar observation has been made by Dupuy,[2] but he does not offer any satisfactory explanation for the phenomenon. The purpose of the present preliminary report is, therefore, to display the characteristic responses of these aberrant T waves of "functional" origin to various procedures, and therefrom not only to elucidate the mechanism underlying their causation, but also to provide a simple means of differentiating them from similar alterations of an organic nature.

MATERIAL

The persons who showed these "functional" precordial T-wave changes were male adults who had been referred for a cardiovascular survey because they manifested either signs or symptoms suggestive of structural cardiovascular disease, but who, on subsequent study, were

found to have functional derangement of the cardiovascular system. They ranged in age from 18 to 35 years; the average age was 27 years. No one body type was encountered consistently; the asthenic, hypersthenic, and intermediate types occurred with about equal frequency.

The symptoms, not all of which were uniformly present in every case, included, aside from nervousness and weakness, (a) dyspnea of the nonhyperventilation type, ranging from a feeling of suffocation to a sensation of not being able to get enough air into the lungs with ordinary respiration; (b) palpitation, usually coming on suddenly and disappearing gradually, but occasionally beginning and ending abruptly; (c) precordial pain, never substernal, not related to exertion, dull and aching in character, limited chiefly to the region of the left nipple, and occasionally associated with "soreness to the touch"; (d) dizziness, not characteristically of the orthostatic type; and (e) pains in various joints unassociated with redness, swelling, or limitation of motion of those structures.

The physical signs, not all of which were uniformly present in every case, consisted of the following: (a) hyperesthesia in the region of the left nipple; (b) a labile blood pressure, with the systolic more variable than the diastolic level; (c) a labile pulse rate which tended to be rapid during waking hours and normal during sleep; (d) systolic murmurs at the base of the heart and sometimes at the cardiac apex, more pronounced when the heart rate was rapid; (e) a poor Schneider index; (f) sighing respiration; (g) cold, sweaty hands; (h) tremors of the outstretched hands; (i) axillary hyperhidrosis during the examination; and (j) ready flushing of the neck and face on slight provocation.

METHOD

Each patient was kept in the hospital long enough to enable the examiners to exclude the possibility of organic heart disease. A careful history was obtained during the first interview, and especial emphasis was placed on factors which might have produced emotional disturbances or an anxiety state. A general assay of the emotional pattern prior to entry into the service was also attempted. In special instances, the assistance of the attending neuropsychiatrist was obtained. A thorough physical examination was conducted immediately after the initial interview, and precautions were taken not to make it appear that the cardiovascular apparatus was being made the object of minute inquiry. In frequent subsequent examinations, the blood pressure and pulse rate in the recumbent and upright positions were carefully checked, systolic murmurs were observed to rule out the possibility of organic valvular disease, hyperesthesia over the precordium was sought for, and the presence of sighing respiration, cold, sweaty hands, tremors, axillary hyperhidrosis, and ready flushing was noted.

In order to obtain corroborative evidence that the heart was not diseased, the following laboratory studies were performed in each case: (a) complete blood cell count, (b) urinalysis, (c) frequent erythrocyte sedimentation rate determinations, (d) a basal metabolic rate estimation, (e) a measurement of blood velocity, and (f) an estimation of cardiac size in the teleoroentgenogram by the method of Ungerleider and Gubner.

In each case, soon after the patient's admission, an electrocardiogram was obtained while he was recumbent and after he had been relaxed

for fifteen minutes and had abstained from smoking for at least thirty minutes. Multiple precordial leads from the left hemithorax were included; an exploring electrode in the C_2, C_3, and C_4 position was paired with the left leg and right arm according to the technique recommended by the American Heart Association.[3] This procedure was repeated at least once every week of the patient's hospital stay. The appearance of an abnormal T wave in any precordial lead was succeeded by the application of the following testing methods, by means of which, in comparable leads, the characteristic responses of the bizarre deflection were graphically recorded:

1. Comparative records were obtained while the patient was recumbent and after the assumption for from three to five minutes of the upright position. Since preliminary studies had indicated that no significant differences are to be noted between the effects induced by a tilt table and those resulting from a postural change accomplished by the subject himself, the latter method was used because of its simplicity. The numbered positions upon the thorax were carefully marked in order to exclude the possibility of malposition of the exploring electrode as a factor in any T-wave alteration resulting from the postural change.

2. The patient then resumed the supine position, and, after he had rested for fifteen minutes, another control tracing was obtained. This was followed immediately by the intravenous administration of 0.5 mg. of ergotamine tartrate, and thirty minutes later, without any change in the position of the patient, a comparable record was recorded.* This interval was selected because preliminary observations[4] had indicated that, in man, the maximum pharmacologic effect of this preparation, which is essentially sympatholytic in character,[5-7] occurs thirty minutes after its exhibition by this route and is sustained usually for sixty minutes longer. In special instances, this procedure was extended to include a record of the effects of postural change while the heart was still under the influence of ergotamine. Also, occasionally, in order to demonstrate the mutually antagonistic influences upon the precordial lead T wave of the sympathetic and parasympathetic components of the autonomic nervous system, tracings were obtained with the subject recumbent while the heart was under the maximal influence of both ergotamine and atropine.† For the latter type of experiment, the effects of ergotamine were registered in the usual manner thirty minutes after its exhibition, immediately after which 2.5 mg. of atropine sulfate were administered subcutaneously, following which successive records were obtained at intervals from fifteen to sixty minutes thereafter.

3. On a different day, a control tracing with the patient recumbent was recorded; the usual precautions regarding relaxation and abstention from tobacco were adhered to. Immediately afterward, 2.5 mg. of atropine sulfate were administered subcutaneously, and then sequential records during recumbency were obtained in successive fifteen-minute intervals for one hour.

4. On another occasion, the sympathomimetic effects of amyl nitrite were registered. The usual control tracing during recumbency was fol-

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*The effect of ergotamine tartrate in this dosage on the normal electrocardiogram of a person with a stable autonomic nervous system consists in a slowing of the sinus rate and a slight increase in the amplitude of the T wave in all leads, without any alteration in the form or direction of this deflection.

†The parasympathomimetic effects of atropine may be evident up to fifteen minutes after the subcutaneous injection of 2.5 mg. of this drug, whereas its parasympatholytic properties become manifest from twenty to sixty minutes after its administration in this dosage.

lowed by the inhalation of 5 minims of this drug, and then a comparable record was obtained with the patient in the same position, after a significant fall in the blood pressure and secondary tachycardia had developed.

RESULTS

Distortions in the precordial lead T waves during recumbency occurred in 80 per cent of the cases which formed the basis of this study. In one-fourth of this number, significant corresponding aberrations of the same deflection were apparent in the limb leads in the same record. The characteristics of these bizarre precordial lead T waves are listed in Table I. It will, in addition, be noted from Table II that it is possible not only to classify them as expressions of autonomic imbalance, but also to identify them more specifically as manifestations of hypervagotonia or hypersympathicotonia because of their responses to the testing methods described in the text.

The inconstancy and variability of the precordial lead T-wave aberration in comparable leads in successive electrocardiograms from the same patient were striking features. In each case, it was definitely ascertained that these variations could not be attributed to malposition of the exploring electrode. Occasionally this instability of the T wave was even apparent in successive cardiac cycles in the same electrocardiogram. Most often, the abnormality of the precordial lead T wave was evident in one or more of the CF leads and absent in corresponding CR leads.

TABLE I

"FUNCTIONAL" PRECORDIAL LEAD T-WAVE ABERRATIONS

TYPE OF ABERRATION	VAGOTONIC	SYMPATHICOTONIC
Variations in successive cardiac cycles	+ +	+ +
Polarity reversal	+ +	+
Inconstancy of T-wave alteration in successive routine electrocardiograms	+	+ +
Notching	−	+ +
Reduced amplitude	+	+ +
Upright with blunting of apex	−	+ +
Associated heart rate	Usually below 75	Always above 75

+ + = Frequently encountered.
+ = Occasionally encountered.
− = Never encountered.

TABLE II

EFFECTS OF TESTING METHODS ON DISTORTION OF T WAVE

	VAGOTONIC	SYMPATHICOTONIC
Upright position (sympathomimetic effect)	−	+
Ergotamine (sympatholytic effect)	+	−
30 to 60 minutes after atropine (parasympatholytic effect)	−	+
Amyl nitrite (sympathomimetic effect)	−	+
15 minutes after atropine (parasympathomimetic effect)	+ or 0	−

+ = Exaggeration of T-wave distortion.
− = Elimination or lessening of T-wave distortion.
0 = No effect upon T-wave distortion.

The spontaneous appearance of vagotonic precordial lead T-wave aberrations was limited to the CF leads in every case, whereas those due to hypersympathicotonia were sometimes seen in both the CF and CR leads. In no instance were any of these unstable T waves limited to the CR leads alone.

In the group with distortion of precordial lead T waves caused by hypervagotonia, a sympatholytic drug, such as ergotamine, made the deformity not only more pronounced, but also more resistant to the usual normalization which resulted from assumption of the upright position. When such deformed, vagotonic T waves spontaneously appeared in one CF lead and not in another, the precordial T wave in the normal CF lead developed some aberration after the administration of this sympatholytic preparation. It was also observed occasionally that distortion of a precordial lead T wave caused by vagotonia spontaneously disappeared in a subsequent record. In such circumstances the original deformity could be reproduced by the administration of ergotamine. A comparable effect was produced by a parasympatholytic drug, such as atropine, when bizarre precordial lead T waves caused by hypersympathicotonia had similarly spontaneously disappeared, with the exception that in the latter group such induced changes were apparent even in leads employing another extremity for the application of the indifferent electrode.

These bizarre precordial lead T waves caused by preponderance of either cholinergic or adrenergic stimuli did not seem to be brought about by changes in the heart rate, although, in some instances, a direct relationship could not be excluded entirely.

ILLUSTRATIVE CASES

CASE 1.—This 22-year-old Negro was admitted to the hospital because of bilateral parotid swelling. The diagnosis of epidemic parotitis was confirmed by the contagion officer. The clinical course of the patient was uneventful, but, during his convalescence, he complained of a fairly constant ache in the region of the left nipple. Careful questioning revealed the fact that this symptom had been present frequently during the preceding three years, had occurred independent of exertion, and was definitely related to disturbed emotional states. However, because of the presence of a systolic apical murmur, he was referred for a cardiovascular survey after he had made a complete and uncomplicated recovery from his attack of mumps.

Examination on the cardiac service elicited the following: The patient was an asthenic, apprehensive person who had a labile pulse rate which tended to be about 60 during rest, axillary hyperhidrosis, and cold, sweaty hands. There was a short, low-pitched systolic apical murmur while he was recumbent, but it disappeared when he sat up, and it did not, even in part, replace the first heart sound. It was therefore considered to be "functional." All laboratory studies and other diagnostic procedures failed to reveal any evidence of acute or chronic heart disease.

Repeated electrocardiograms while he was recumbent consistently revealed inversion of the T wave in Lead CF_2, without any accompany-

ing T-wave changes in the limb leads or in the other chest leads (Figs. 1, 2, and 3). On different occasions, the amplitude of this negative precordial lead T wave varied in depth (Figs. 1, 2, and 3). The response of this bizarre precordial lead T wave to the various testing procedures was as follows: The upright position converted it to a positive deflection. This occurred either when the patient was tilted to a perpendicular position (Figs. 2 and 3), or when he assumed the vertical position himself (Fig. 1). Atropinization, after thirty minutes, independent of any postural change, produced a similar effect, but not to a comparable degree (Fig. 1). Amyl nitrite during recumbency produced an effect similar to that brought about by the upright position (Figs. 1 and 3). Ergotamine, with the patient in the recumbent position, had no significant effect on the inverted T wave in Lead CF_2, but it did convert the positive T wave in Lead CF_4 to a negative deflection (Fig. 1).
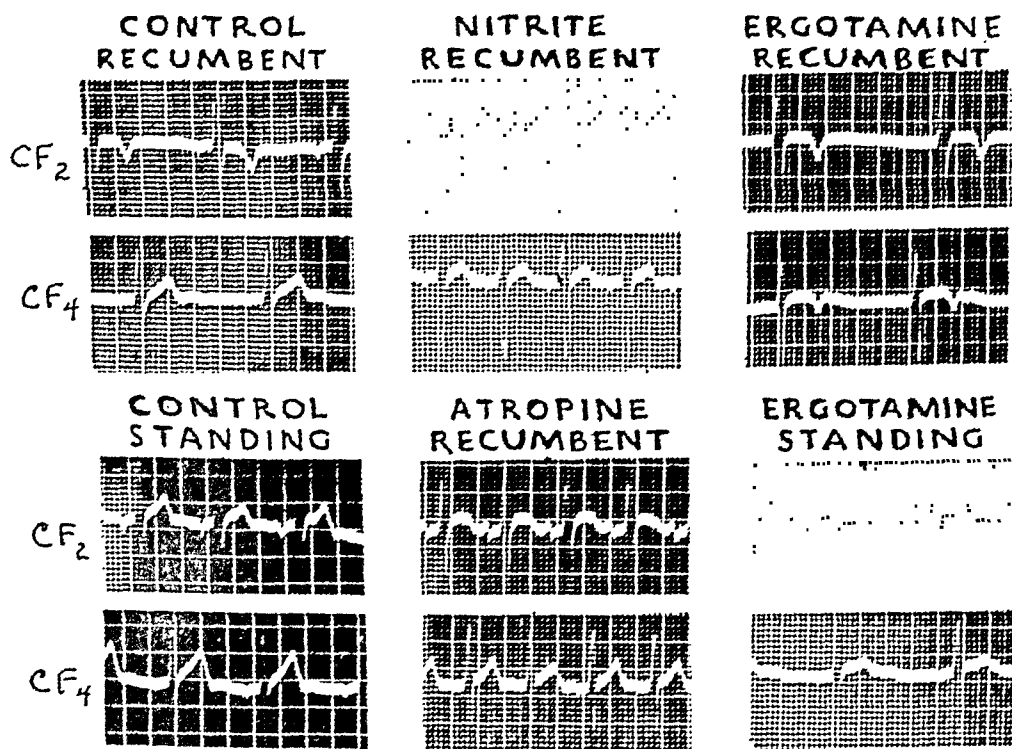
Fig. 1.—Case 1.

Also, while the heart was still under the influence of ergotamine, the assumption of the upright position did not cause the usual reversion of the T wave in Lead CF_2 to a positive deflection (Fig. 1). In addition, with the heart under these combined influences, the T wave in Lead CF_4, although positive in direction, was definitely depressed as compared with the amplitude it attained in control electrocardiograms obtained in the upright position (Fig. 1).

Comment.—The characteristic response in this instance of the bizarre T wave in Lead CF_2 to sympathomimetic and parasympatholytic influences establishes the fact that it was merely a manifestation of hypervagotonia. The ability of a sympatholytic drug, such as ergotamine, not only to prevent the usual effect of the upright position on the in-
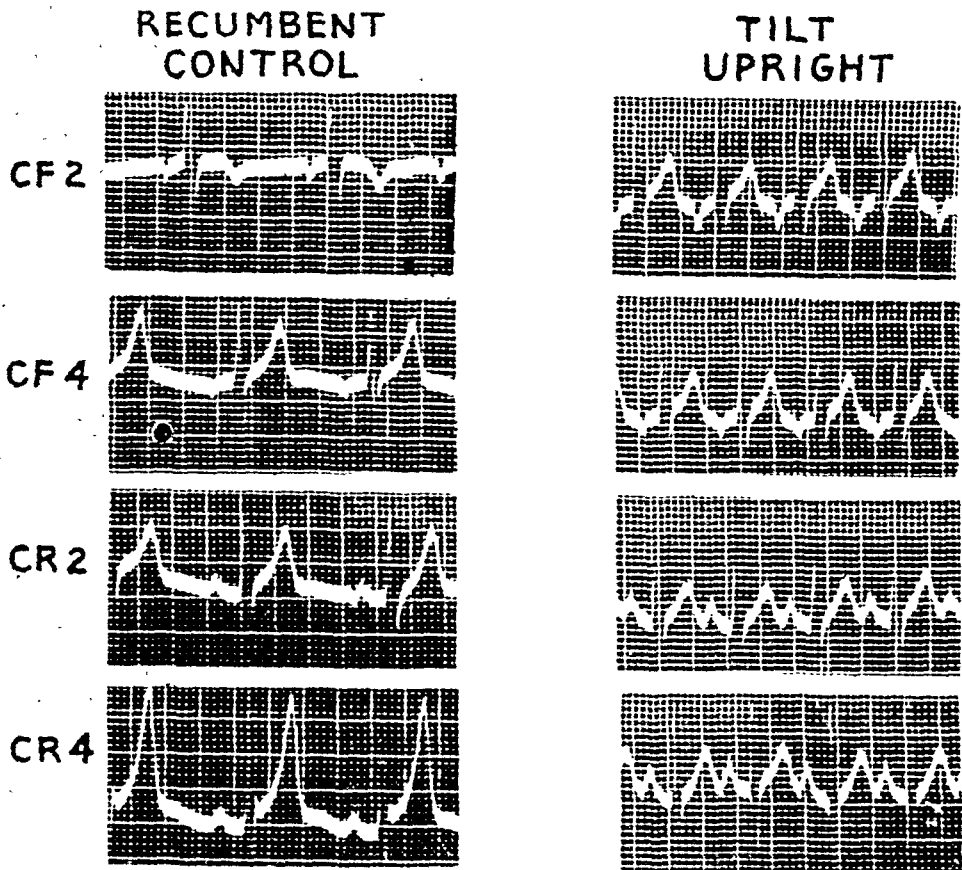
Fig. 2.—Case 1.
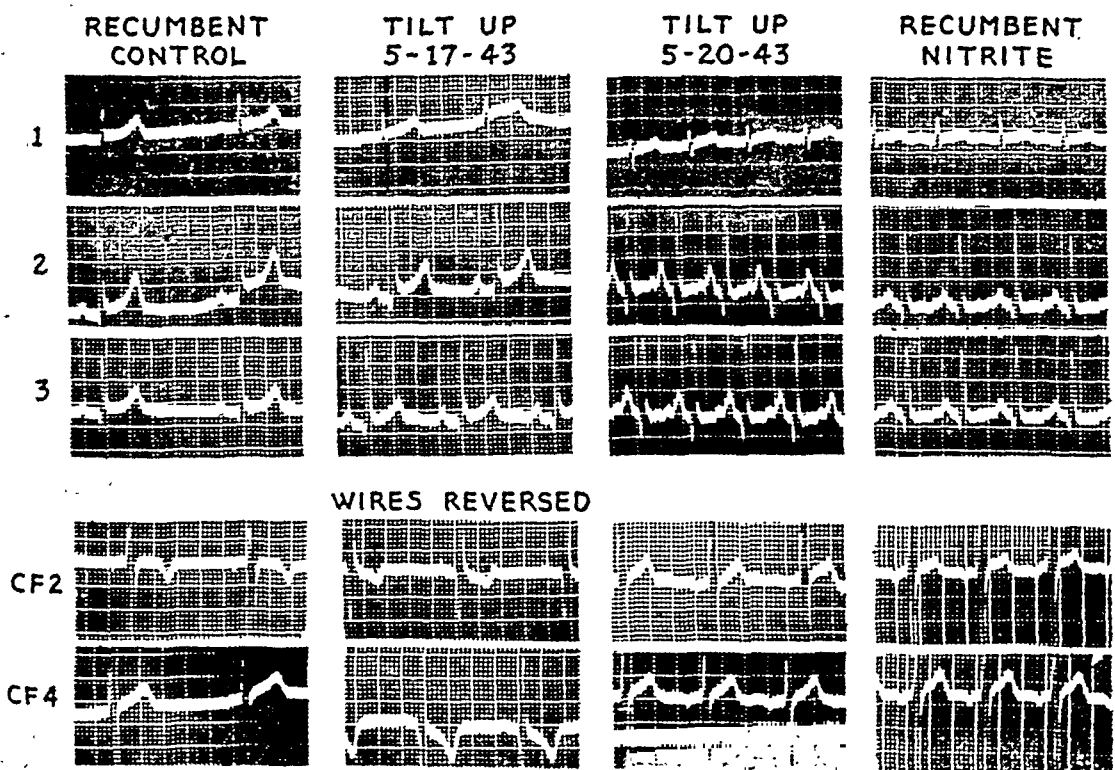
Fig. 3.—Case 1.

verted T wave in Lead CF_2, but also to produce T-wave distortion in Lead CF_4 in the recumbent position is further evidence in support of this view. The latter experiment, in addition, shows conclusively that any T-wave alteration produced by assuming the upright position is to be attributed to increased sympathetic tone, reflexly induced, and not to a change in the position of the heart. Also in favor of this hypothesis are the observations that, in the same case, amyl nitrite, during recumbency, produced T-wave changes in both the limb and precordial leads which were indistinguishable from those resulting from a change in direction of the long axis of the body (Figs. 1 and 3), and that the upright position did not produce polarity changes in the T waves of the limb leads when tachycardia did not occur (Fig. 3). On the contrary, the reversal of the vagotonic inverted T wave in Lead CF_2 to positive polarity as a result of postural change bore no relation to the heart rate (Fig. 3), indicating the fundamental instability of such functionally bizarre precordial lead T waves.

Also, the influence of heart rate in the production of the bizarreness of the precordial lead T wave in this instance appears to be unimportant. The inversion of the T wave in Lead CF_4 caused by a sympatholytic drug (Fig. 1) was associated with a heart rate no slower than that concurrent with a normal T wave in the same lead in a control tracing on a different occasion (Fig. 3), and the positive T wave in Lead CF_2 resulting from assumption of the upright position (Fig. 3) was not associated with a heart rate any more rapid than that which accompanied an inverted T wave in the same lead in a control record obtained at another time in the recumbent position (Fig. 2).

CASE 2.—This 18-year-old white man was referred to the cardiac service because a systolic murmur was discovered during his stay in the hospital for an acute upper respiratory infection. No history of antecedent rheumatism or recent polyarthritis could be elicited. Examination revealed the following: The patient was a tall, well-nourished man who was apprehensive, flushed easily, and had cold, sweaty hands, a labile pulse rate, a labile blood pressure, tremors of the outstretched palms, and axillary hyperhidrosis. He admitted being emotionally disturbed, and stated that at one time it was thought that he was developing a "code neurosis." A short, low-pitched systolic apical murmur was heard during recumbency, but it disappeared when the patient assumed the upright position, and it did not even in part replace the first heart sound. It was therefore considered to be "functional." All laboratory studies and other diagnostic procedures failed to reveal any evidence of acute or chronic heart disease.

Electrocardiograms during recumbency on various occasions revealed an inconstant inversion of the T wave in Lead CF_2, independent of any accompanying T-wave changes in the limb leads or other precordial leads (Figs. 4, 5 and 6), and by careful checking it was made certain that these T-wave alterations could not be ascribed to malposition of the exploring electrode.

The response of this bizarre precordial lead T wave to the various testing procedures was as follows: The upright position converted it to

a positive deflection (Fig. 4). Amyl nitrite during recumbency had a similar effect (Fig. 4). On an occasion, when the T wave was diphasic, ergotamine exaggerated the bizarreness of this deflection, transforming it into a deeply inverted T wave (Fig. 5). Although the upright position did result in a reversal to positive polarity of this ergotamine-induced precordial lead T-wave deformity, this reversal did not occur
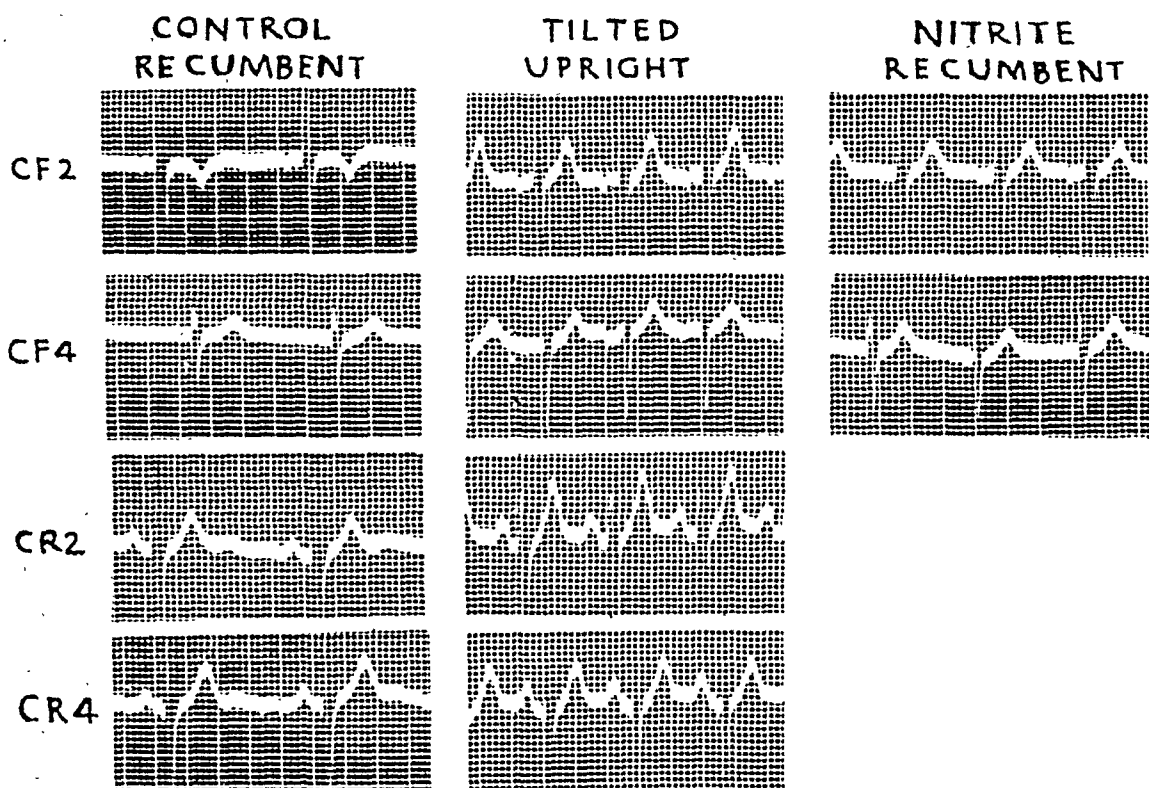
Fig. 4.—Case 2.
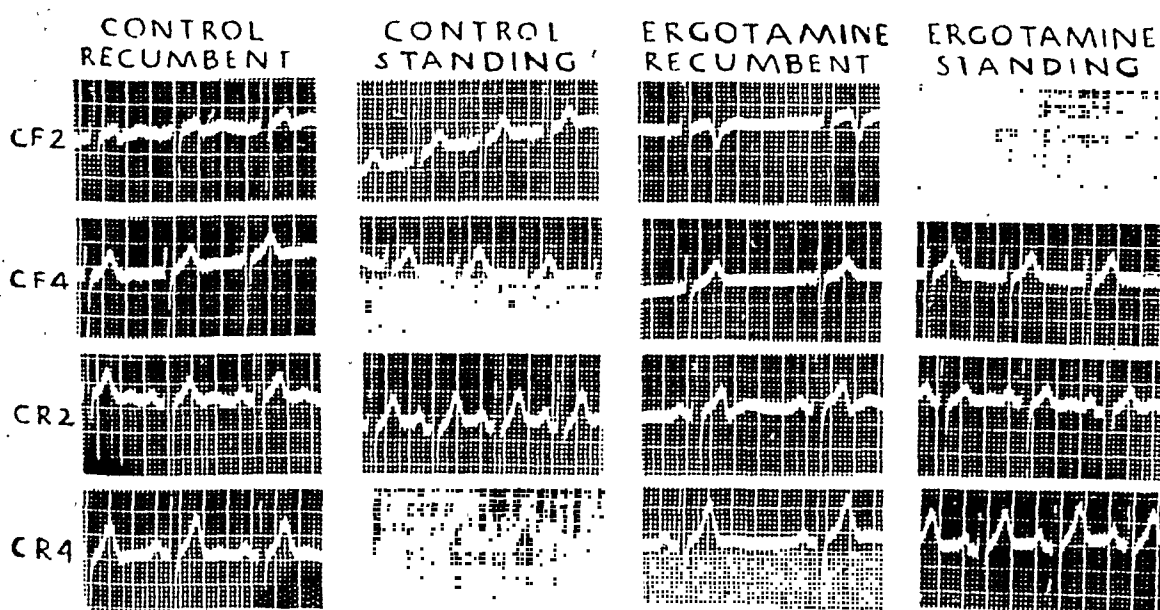
Fig. 5.—Case 2.

to the same extent as that which had been brought about by the postural change immediately prior to the exhibition of this drug (Fig. 5). On another occasion, when the T wave in CF_2 in the control record had spontaneously become normally upright, ergotamine produced a similar

change (Fig. 6); this, in turn, was abolished by the parasympatholytic action of atropine, even while the heart was still under the influence of the former drug (Fig. 6).

Comment.—The characteristic responses of the bizarre T wave in lead CF_2 to sympathomimetic influences (Fig. 4) undoubtedly indicate that this electrocardiographic alteration merely represented vagal preponderance. The nonpersistence of the abnormal T wave in repeated records (Figs. 4, 5, and 6) undoubtedly means that, even in those unstable persons whose vagotonic electrocardiographic pattern is a characteristic feature, the level of "cholinergia" is not constant. For this reason, the instability of the precordial lead T wave obviously is to be related to variations in nerve tone. This concept is an important one, for it can be usefully applied to the proper appraisal of spontaneous fluctuations in form, amplitude, and polarity of the precordial lead T wave in successive electrocardiograms on anyone who presents the stigmas of a functional, rather than an organic, derangement of the cardiovascular system.

| | CONTROL RECUMBENT | ERGOTAMINE RECUMBENT | ERGOTAMINE ATROPINE |
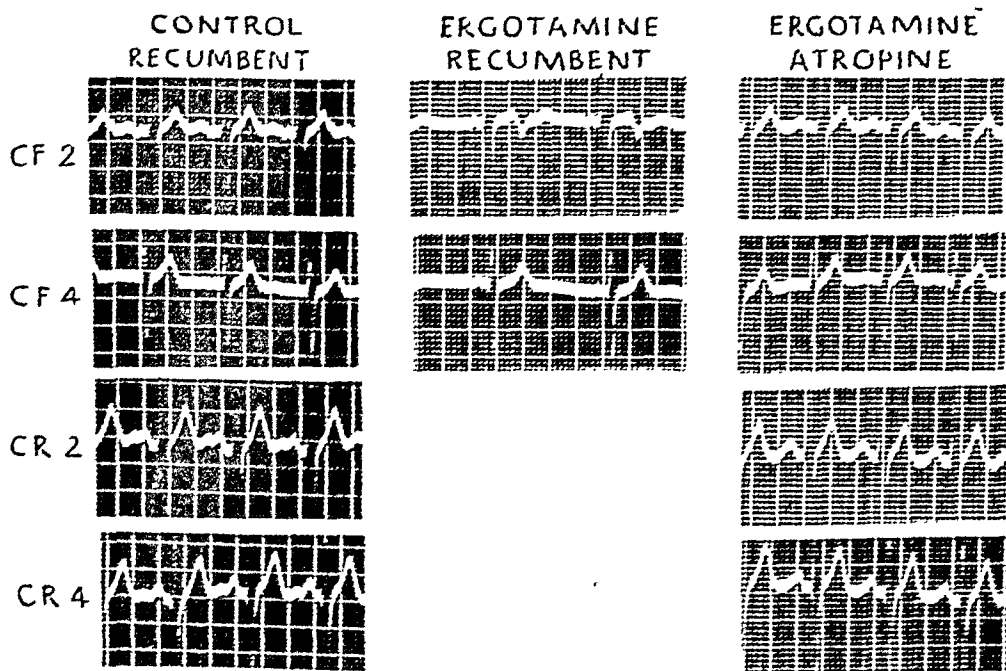
Fig. 6.—Case 2.

Another interesting observation in the study of this case was the fact that, even under circumstances in which hypervagotonia existed in a "latent" stage, such inherent instability of the autonomic nervous system could be made apparent in the electrocardiogram after the supplemental administration of a sympatholytic preparation such as ergotamine (Fig. 6). This phenomenon is especially significant because this drug acts upon the T wave in a directly opposite manner in stable individuals.[4]

Although variations in the degree of aberration in the precordial lead T wave were evident in repeated curves (Figs. 4, 5, and 6), instability of this deflection was seen even in successive cardiac cycles in the same electrocardiogram (Fig. 5). This was not uncommon in the entire group.

It will be noticed that comparable effects were produced by amyl nitrite during recumbency and by the upright position (Fig. 4). This again indicates that the postural change produces its effects, not by a change in the position of the heart, but by a reflex increase in sympathetic tone. This phenomenon likewise serves to show how easily the precordial lead T wave of an unstable person can be influenced by a slight preponderance of one or the other components of the autonomic nervous system, in contrast with the stability of this deflection in the precordial leads from normal adults when the upright position is assumed.[4]

As in the preceding case, the effects of vagal preponderance on the precordial lead T wave were displayed only in a CF lead (Figs. 4, 5, and 6).

The relation of heart rate to the appearance of a bizarre precordial lead T wave appeared to be, in this instance, a close one, for the deflection was most abnormal when the rate was 60 or below, regardless of whether this associated bradycardia occurred spontaneously in a control record (Fig. 4) or whether it was a part of an ergotamine effect (Figs. 5 and 6).

CASE 3.—This 28-year-old white man was referred to the cardiac service because hypertension had been found during a routine examination prior to being commissioned. His complaints consisted of shortness of breath, palpitation, precordial pain, excessive sweating, dizziness, and nervousness. He stated that he had always been "high strung," and admitted that at one time the diagnosis of "code neurosis" had been considered. Examination revealed the following: The patient was a well-nourished man with an intermediate type of habitus, who flushed easily, was apprehensive, and had a labile pulse rate and a labile blood pressure, tremors of the outstretched hands, and axillary hyperhidrosis. Nothing significant was revealed by examination of the heart. All laboratory studies and other diagnostic procedures failed to reveal any evidence of acute or chronic heart disease.

Repeated electrocardiograms exhibited variations in the precordial lead T waves, characterized chiefly by a reduction in the amplitude and by notching of the apex (Fig. 7). Occasionally, actual inversion of the T wave occurred, especially in the upright position. These changes, but not to the same degree, appeared in all the chest leads and frequently were associated with alterations of the same order in the limb leads. The response of these bizarre precordial lead T waves to ergotamine was normalization of their configuration (Fig. 7).

Comment.—The characteristic response, in this instance, of the bizarre precordial lead T waves to sympathomimetic influences and to a sympatholytic drug establishes them definitely as expressions of adrenergic preponderance. The resemblance of these "functional" distortions of

the T wave to those produced by structural disease is striking. In this case, the occurrence of changes in the CR and limb leads similar to those which were present in the CF leads was not unexpected, because such associated changes seem to be the rule in the "sympathicotonic" group, as contrasted with the absence of such combined alterations in the "vagotonic" group. In this case, too, there were spontaneous fluctuations in the degree of aberration of these T waves in repeated curves, and, because of the symptoms and physical signs, the electrocardiographic changes were originally construed to be evidences of active carditis. However, the application of the testing methods described in the text eventually permitted a proper appraisal, and the conclusion that they were an indication of a functional cardiac derangement was subsequently confirmed by the clinical course.
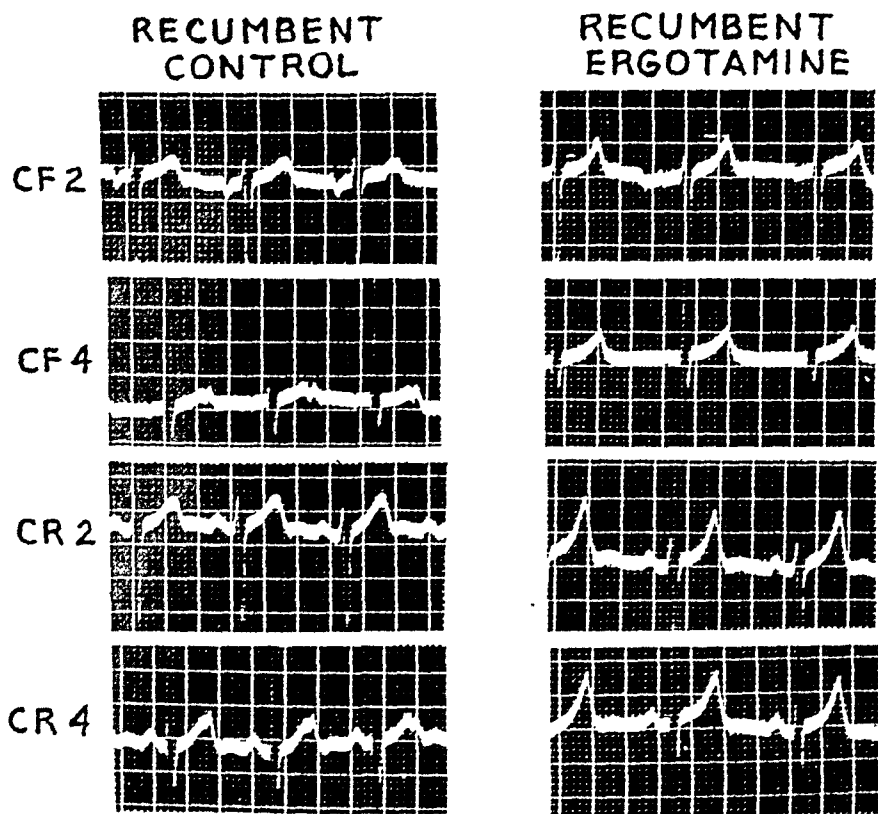
Fig. 7.—Case 3.

The relation of heart rate to the appearance of a bizarre precordial lead T wave in this instance did not appear to be close because spontaneous aberrations in this deflection in the recumbent position were frequently of a higher degree when the rate was below 85 than when it exceeded this level.

CASE 4.—A 21-year-old white man was referred to the cardiac service because of an attack of rapid heart action of several hours' duration. The patient stated that he had suffered similar attacks of tachycardia,

characterized by an abrupt onset and abrupt termination, frequently since his adolescence. The precipitating cause was not always evident, but emotional crises seemed to be an important etiological factor. He admitted that he was always a "nervous" person, and that he was easily disturbed emotionally by even relatively insignificant events. Examination revealed the following: The patient was a moderately well-nourished person with an intermediate type of habitus, who flushed easily,

RECUMBENT   STANDING

CF2

CF4

CR2

CR4

Fig. 8.—Case 4.

| RECUMBENT CONTROL | ERGOTAMINE 30 MIN. | ERGOT.-60 MIN. ATROPINE-15 MIN. | ERGOT.-90 MIN. ATROPINE-45 MIN. |

CF2

CF4

CR2
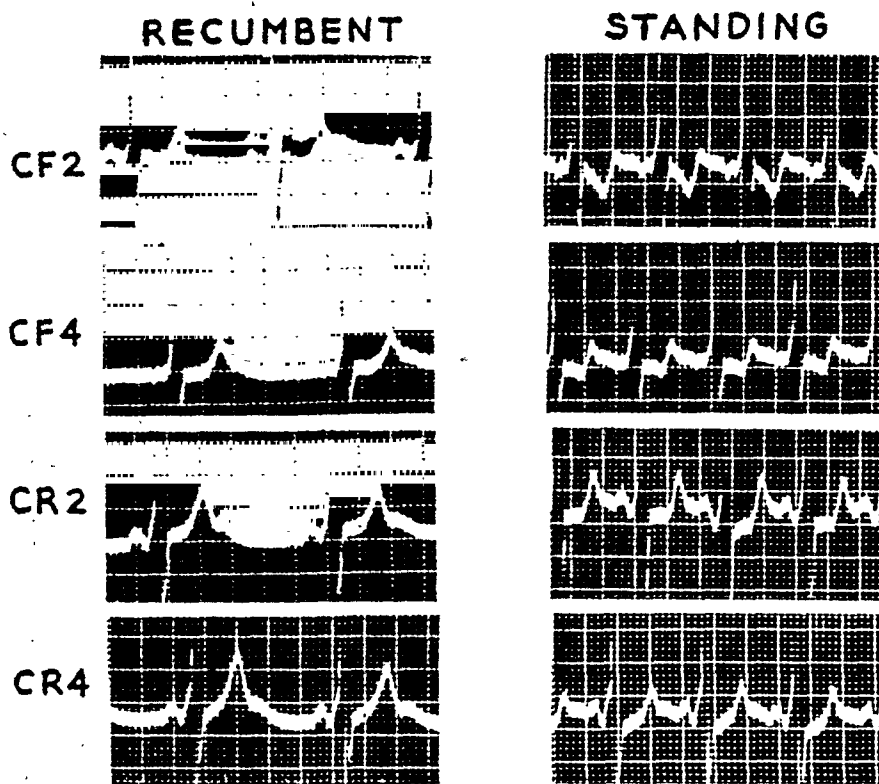
CR4
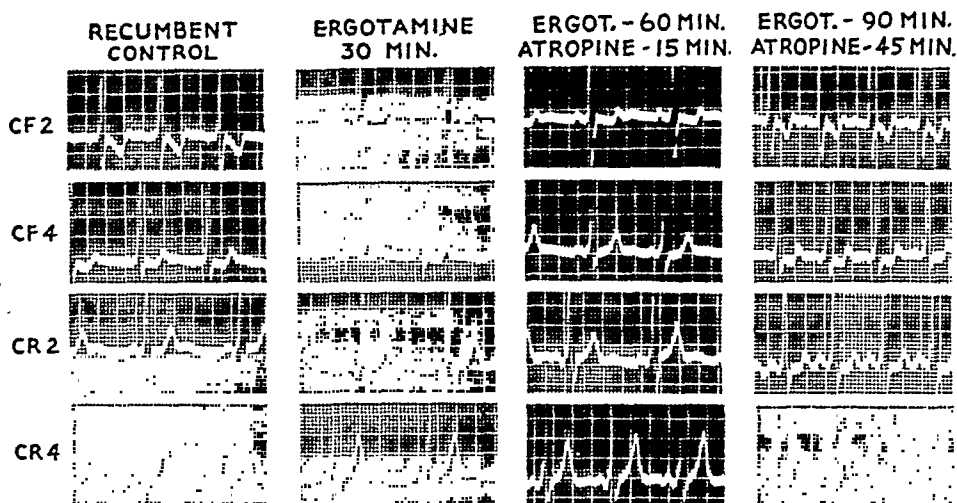
Fig. 9.—Case 4.

was apprehensive, and had a labile pulse rate and a labile blood pressure, tremors of the outstretched hands, axillary hyperhidrosis, and cold, sweaty palms, and who manifested sighing respiration at frequent intervals. Nothing significant was revealed by examination of the heart. All laboratory studies and other diagnostic procedures failed to reveal any evidence of acute or chronic heart disease.

·Electrocardiograms, obtained at frequent intervals, revealed inconstant inversion of the T wave in Lead CF_2 (Figs. 8, 9, and 10). In addition, there were constant shortening of the P-R interval and slurring of the upstroke of the R wave; this was diagnostic of the Wolff-Parkinson-White syndrome (Fig. 8). No comparable changes in the T wave occurred in the limb leads at any time. Occasionally, depression of the S-T segment, with a tendency to a diphasic configuration of the T wave, was apparent in Lead CF_4 (Figs. 9 and 10). The response of the precordial lead T wave to postural change, which was recorded at a time when the T wave in the control record had spontaneously reverted to normal, took the form of a marked change in polarity of this deflection in Leads CF_2 and CF_4 and a depression of the S-T segments in Leads CR_2 and CR_4 (Fig. 8). On other occasions, a spontaneously appearing deformity of the T wave in Lead CF_2 disappeared thirty minutes after the administration of ergotamine (Fig. 9) and fifteen minutes after the administration of atropine (Fig. 10). The normalization of the T wave in Lead CF_2 by ergotamine did not persist forty-five minutes after the exhibition of atropine, even though during this time the heart was still under the influence of the former drug.
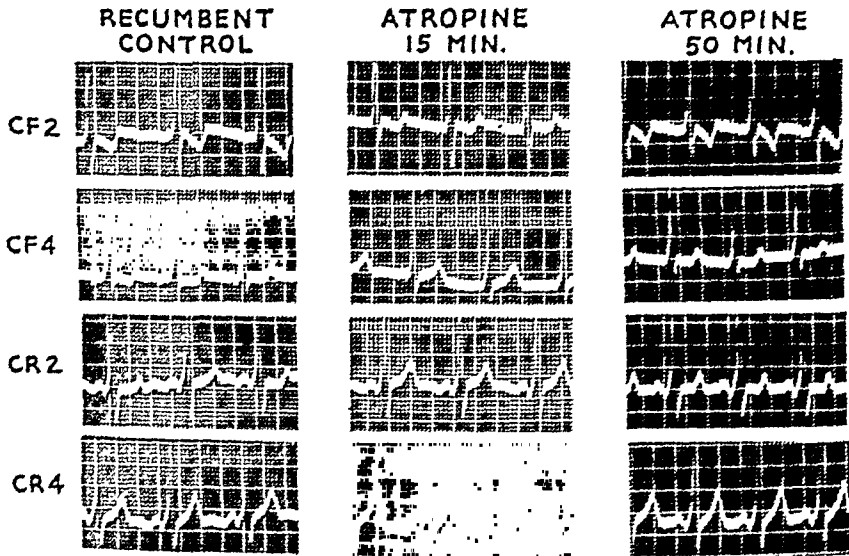
Fig. 10.—Case 4.

Comment.—The spontaneous fluctuations in the polarity of the precordial lead T waves and configuration of the S-T segments were a striking feature in this case, and, in this respect, were characteristic of the behavior of the functionally unstable deflections described in this report. The typical response to postural change (Fig. 8), to a sympatholytic drug (Fig. 9), and to the parasympathomimetic effect of atropine (Fig. 10) establishes the fact that the instability is caused by a state of adrenergic preponderance. The mutually antagonistic influences of the vagal and sympathetic components of the autonomic nervous system on the S-T-T portion of the precordial electrocardiogram are well illustrated in the experiment in which the parasympatholytic effects of atropine became evident while the heart was still under the influence

of a sympatholytic drug such as ergotamine (Fig. 9). Although the presence of the Wolff-Parkinson-White electrocardiographic pattern in this case supplies an explanation for the attacks of tachycardia, there was no apparent relationship between this anomaly and the presence of the unstable precordial lead T waves.

The relation of heart rate to the appearance of the sympathicotonically distorted precordial lead T waves is presumably not a close one, for, at times, a normalization of this deflection was accompanied by a rate more rapid than that associated with a distortion of the same wave (Fig. 10).

<div align="center">DISCUSSION</div>

In previous reports, other investigators have already described electrocardiographic aberrations in cases of neurocirculatory asthenia.[8, 9] These have consisted of S-T segment depressions and T-wave inversions in the limb leads, when the electrocardiogram is made with the subject in the semi-erect[8] or upright position.[9] However, these alterations are of questionable significance, for it has been demonstrated that identical changes may occur in normal, emotionally stable persons,[4, 10] presumably because of a reflex discharge of adrenergic stimuli which results physiologically from the vertical projection of the long axis of the trunk,[4, 10, 11] and not, as maintained by some,[12, 13] because of changes in the position of the heart. Inasmuch as the stability of the precordial lead T wave in normal subjects is unaffected by such postural change,[4] in contrast with the opposite behavior of the same deflection in the limb leads, the observations, in the present study, of precordial lead T-wave aberrations even during recumbency in cases of "functional" heart disease can be considered not only unique but also of real diagnostic import.

Although the precordial lead T-wave deformities in the cases which formed the basis of the present study have been shown to be due to preponderance of either vagal or sympathetic tone, their resemblance to abnormalities which result from structural cardiac disease is evident. It is for this reason that the interpretation of any distortion of a precordial lead T wave, especially in cases in which the symptoms or signs are merely suggestive of the presence of genuine heart disease, must ultimately depend on a proper assay of these factors. This view is shared, but only in part, by Nordenfelt,[11] for he believes that heightened sympathetic tone alone can cause "functional," spontaneous aberration of a precordial lead T wave, and therefore concludes that any abnormality of this deflection (with the subject recumbent) which is not abolished by a sympatholytic drug, such as ergotamine, shall be construed as indicative of organic heart disease. However, the observations in Cases 1 and 2 suggest the need for extending the concept of the close relationship of autonomic imbalance to "functional" T-wave distortions to include the role of heightened vagal tone, as well.

The testing methods which have been developed in order to permit a proper evaluation of the extent to which an alteration of a precordial lead T wave represents an expression of tonal preponderance of either of the components of the autonomic nervous system are carefully described in the text of this critique. By this means it is possible to attribute to vagotonic influences any aberration of this deflection which is exaggerated by a sympatholytic drug and abolished by parasympatholytic and sympathomimetic drugs or by the assumption of the upright position, whereas an altered T wave which is normalized by a sympatholytic drug and exaggerated by a sympathomimetic drug or the assumption of the upright position can be related to increased sympathetic tone (Table II). Aside from their simplicity and harmlessness, these procedures have been found ideal for the purpose because of the fact that similar T-wave alterations which are due to structural changes remain unaffected by them.[4]

However, even if a deformed precordial lead T wave, by its characteristic responses to these simple procedures, can be properly identified, the cause of the underlying imbalance of the nervous control of the heart needs also to be established. The excessive discharge of adrenergic or cholinergic stimuli which is known to accompany disturbed emotional states in animal experiments[14, 15] suggests that emotional instability may prove to be the dominant factor in the production of such unstable T waves in man. Their frequent occurrence in the cases of neurocirculatory asthenia described in this report would seem to support this view. This opinion is also inferentially corroborated by a critical examination of Nordenfelt's data,[11] which indicates that the "sympathicotonic" T waves which he describes can be correlated with various types of functional disease.

Moreover, spontaneous fluctuations in the form, amplitude, and polarity of a vagotonic or sympathicotonic precordial lead T wave in successive electrocardiograms on the same subject was a characteristic feature in the cases which formed the basis of this study. Since malposition of the exploring electrode was excluded as a causative factor, the likely explanation for this phenomenon is the occurrence of a variation in the degree of autonomic nervous dysfunction arising from variations in the intensity of the emotional disturbance. It is therefore important not to disregard this possibility lest a mistaken diagnosis of acute myocardial change be made, especially when arthralgias, a systolic murmur, and precordial pain are associated manifestations of the syndrome.

It has also been observed that the T-wave representation of autonomic imbalance in the human electrocardiogram may occasionally disappear spontaneously and completely, in both the "vagotonic" and "sympathicotonic" groups (Cases 2 and 4). Under such circumstances, the use of an appropriate drug or maneuver will result in a distortion of

the precordial lead T wave analogous to that which had been apparent in the same case in a routine tracing at a previous time (Case 2, Fig. 6; Case 4, Fig. 8). The implications of this phenomenon are far-reaching. For one thing, it would seem that a dysfunction of the autonomic nervous system can never be entirely dismissed, even when all the electrocardiographic deflections in a single, routine record are normal, unless a "latent" preponderance of the cholinergic or adrenergic components can be excluded by supplemental studies following the administration of sympatholytic or parasympatholytic drugs, respectively. Other advantages in the use of this simple method for the identification, through the medium of the human electrocardiogram, of a "latent" imbalance of autonomic function in man will be more fully dealt with in a subsequent paper.

The relation of heart rate to the appearance or disappearance of aberrant T waves due to excessive adrenergic or cholinergic impulses cannot be stated with finality at this time. Most often, but not always, a "vagotonic" T wave, when it occurred spontaneously, was associated with a relatively slow rate (Table I); when it was exaggerated by ergotamine, it was accompanied by bradycardia; and, when it was abolished by parasympatholytic or sympathomimetic procedures, the influence of cardiac acceleration could not be entirely discounted. On the contrary, the appearance of a "sympathicotonic" T wave was not always associated with tachycardia, and the elimination of such a deformity by ergotamine was not always dependent on the development of bradycardia. In any event, it appears to be true, in the present group, that the occurrence of a bizarre T wave, whether it be due to vagotonia or sympathicotonia, cannot be correlated with a critical heart rate in the same person. The parallelism sometimes seen may be coincidental, in that both are independent effects of nerve tone. The rate, therefore, can be considered only another measure of the degree of nerve tone dominance.

The mechanism by which the precordial lead T wave is as greatly distorted in cases of neurocirculatory asthenia as in instances of structural cardiac disease will require further study. It is possible that the phenomenon may be related to a disturbance of ionic equilibrium in the cellular electrolytes, which is known[16] to result from overexcitation of one or the other components of the autonomic nervous system in response to various emotional stimuli. Conceivably, the summated electromotive forces which are projected in the preterminal deflection of the human electrocardiogram may be sufficiently altered by this means to produce the T-wave changes encountered in these instances. In any case, it can be categorically stated, from the evidence at hand, that the balanced dualistic role of the autonomic nervous system in the preservation of cardiac homeostasis is important not only because of the regulatory control it exercises upon the rate, rhythm, and conduction, but also

because of its modifying influence upon the electrical events which accompany cardiac muscle contraction. The prediction can therefore be ventured that recognition of the contribution of autonomic nervous stimuli to this latter function undoubtedly will prove of assistance in the appraisal of heretofore obscure phenomena in the human electrocardiogram.

SUMMARY AND CONCLUSIONS

1. It is shown that multiple precordial leads derived from the left hemithorax of the recumbent subject suffering from "functional" heart disease may reveal alterations in form, amplitude, and polarity of the T wave which are indistinguishable from those associated with structural cardiac disease.

2. The role of heightened vagal tone or of sympathetic tonal preponderance in the production of these abnormalities of the precordial lead T wave is demonstrated. It is therefore urged that, in the evaluation of any bizarre T wave in the precordial or limb leads when the subject is recumbent, the factor of autonomic imbalance should always be considered.

3. Simple testing methods based on procedures which cause sympathomimetic, sympatholytic, parasympathomimetic, or parasympatholytic effects are described for differentiating these "functional" T-wave alterations from similar changes caused by organic heart disease. It is therefore advocated that these testing methods be applied to every electrocardiogram in order to permit a proper appraisal of any potential or manifest T-wave abnormalities.

4. The demonstration through the medium of the human electrocardiogram of a state of "latent" vagotonia or sympathicotonia is briefly discussed.

5. The instability of these bizarre precordial lead T waves of "functional" origin in successive cardiac cycles in the same electrocardiogram or in successive electrocardiograms in the same case is demonstrated. The importance of recognizing this characteristic feature in the electrocardiograms of persons with "functional" heart disease is emphasized. Methods for avoiding the mistake of attributing these changes to active heart disease are described.

6. The importance of emotional factors in the production of "functional" precordial lead T-wave distortions is stressed.

7. The relation of heart rate to the occurrence or disappearance of these "functional" aberrations of the precordial lead T wave is considered.

8. The mechanism by which vagotonic or sympathicotonic influences can alter the preterminal deflection of the human electrocardiogram is briefly discussed.

9. The importance to the Armed Forces of recognizing these unstable precordial lead T waves, because of their relation to neurocirculatory asthenia, is stressed.

10. Evidence is presented to indicate that the balanced dualistic role of the autonomic nervous system in the preservation of cardiac homeostasis is important not only because of the regulatory control it exercises upon the rate, rhythm, and conduction, but also because of its modifying influence upon the electrical events which accompany cardiac muscle contraction.

11. The timeliness of these observations is evident because the recent recommendations of the American Heart Association for the routine employment of multiple precordial leads was prompted primarily by a desire to increase the usefulness of the electrocardiograph in the diagnosis of structural cardiac disease.

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THE RELATIONSHIP OF BLOOD VISCOSITY TO THE INTENSITY OF HEART MURMURS

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LATE in 1942, a patient with polycythemia was admitted to the New York Hospital. His erythrocyte count was 9,000,000, his hemoglobin, 23.8 Gm. (165 per cent), and his hematocrit, 79 per cent. The bone marrow showed no evidence of polycythemia vera. The electrocardiogram indicated a congenital defect, and the roentgenogram showed a tremendously enlarged pulmonary conus. However, no murmur could be heard. Because of the absence of a murmur, the possibility of polycythemia due to a congenital heart lesion was ruled out. In the light of this interpretation, further observations were indicated to ascertain more precisely the character and extent of the changes in murmurish sounds produced by alterations in the viscosity of the blood.

METHOD

A modification of the Wiggers[1] circulation machine was used. A constant-speed electric motor drove the machine, which was adjusted to pump at a rate of 50 strokes per minute and at a constant stroke volume of 30 c.c. A system of valves prevented backflow, and the circulating medium passed through thick rubber tubing, representing the blood vessels.

Sounds simulating murmurs of cardiac origin were produced by causing blood to pass through a 1 cm. copper tube, closed at one end except for three small openings, each 2 mm. in diameter. This end of the copper tubing was enclosed in a thickwalled rubber tube, 3 cm. in diameter, from which the blood returned to the pump. By this arrangement, turbulence in the flow of blood was produced as it passed through the openings in the copper tubing and into the larger rubber tube. The oscillations so produced in the fluid caused the walls of the rubber tube to vibrate.

A rubber nipple was glued to the 3 cm. tube, just above the three openings in the copper tube. A stethoscope or a microphone was fitted into the rubber nipple, forming an airtight seal. By this means the sounds produced were picked up (Fig. 1).

The amplification and recording systems were made up as follows: a microphone was connected to a specially designed amplifier system, which, in turn, was connected to a loud-speaker. The vibrations of the armature of the loud-speaker were transmitted by a thin copper wire to a small mirror. A beam of light from a projector was reflected from the mirror, and recorded by means of a photokymograph. This system was capable of reproducing frequencies up to 500 cycles per second. The murmurs produced had frequencies under 100 cycles per

second; therefore, the amplifier system was fully adequate to the requirements of this study.

The system was insulated as well as possible against extraneous sounds and electrical fields. Amplification was kept constant.

At all times during the experiments the systolic pressure was kept constant by varying the resistance with a screw clamp beyond the source of the murmur. Since temperature affects the viscosity of blood, it was maintained in these experiments at 20° C.

The circulating medium consisted of Group A bank blood from which most of the plasma had been removed. For the initial observations, blood was used with a hemoglobin level of 140 per cent and an erythrocyte count of 6.9 million. After recordings had been made, the viscosity was lowered, by adding plasma and saline, to 120 per cent hemoglobin, without stopping the circulation in the machine, and with special care not to introduce air bubbles. Thirty minutes were allowed for thorough mixing before taking samples for hemoglobin determination. Recordings of the sounds were then made. This procedure was repeated at hemoglobin levels of 115 per cent, 105 per cent, 90 per cent, and 70 per cent. From ten to thirty sound cycles were recorded and averaged at each level. Additional evidence in corroboration of the observations was obtained by auscultation, and also by increasing the viscosity of the blood through adding more corpuscles.
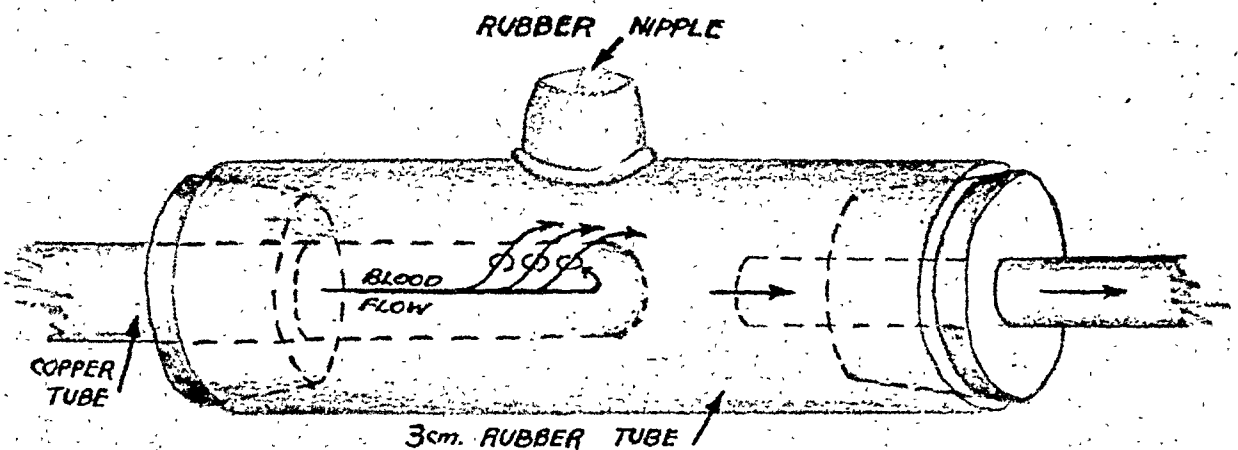
Fig. 1.—Drawing of apparatus used to produce the murmur.

The viscosity of samples of the circulating blood was ascertained by measuring the time taken by 25 c.c. of blood in a filled 50 c.c. burette to pass through a capillary tube, as compared with measurements made in the same way with distilled water.

The criterion used for the intensity of a murmur was the distance from the peak of the fourth highest to the peak of the fourth lowest line in the same records. When this criterion is used, the results of averaging several series of three groups of ten successive murmurs show a deviation of less than 3 per cent for the average of ten cycles. The noise level of the amplifying and recording apparatus was found to be 6 mm., caused by ''AC hum'' of the radio and electrical interference

of the motor, even when no blood was flowing through the apparatus. This 6 mm. level was therefore the zero point in measuring murmur intensities.

RESULTS

With a hemoglobin level of 140 per cent and an erythrocyte count of 6.9 million, no murmur could be detected, either in the records or by auscultation. At 120 per cent hemoglobin, a very faint murmur was detected by the increased amplitude of the vibration. The murmur

HEART SOUNDS IN A HEALTHY YOUNG ADULT

ARTIFICIAL MURMUR   HB 70%

HB 90%

HB 105%

HB 115%

HB 120%

HB 140%
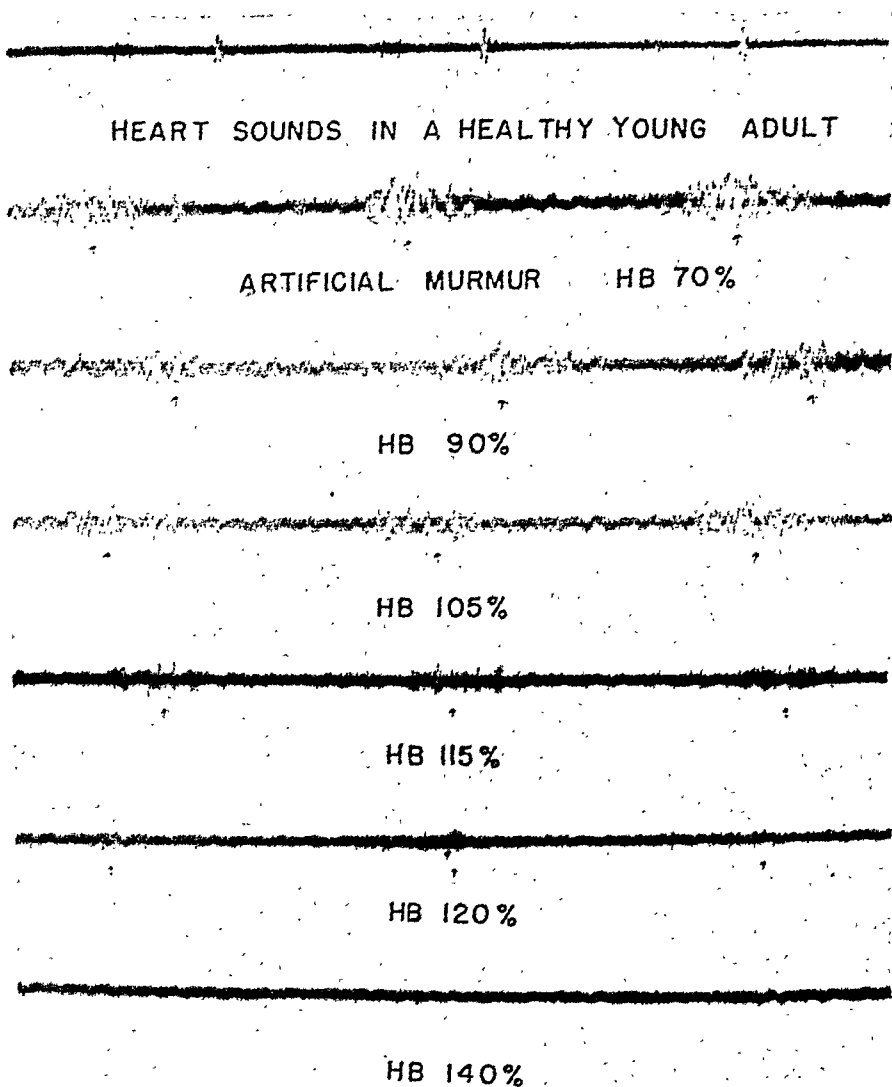
Fig. 2.—Comparison of recordings of normal sounds and artificial murmurs. All recordings are made at the same amplification (×1/3).

grew progressively louder as the blood was diluted, until, at a hemoglobin level of 70 per cent, it was louder than normal heart sounds over the pulmonic area (Fig. 2). Below a hemoglobin level of 70 per cent, no change in the intensity of the murmur could be found. The intensities of the murmurs were measured, tabulated, and plotted.

TABLE I

HEMOGLOBIN LEVEL (%)	MURMUR INTENSITY (MM.)	VISCOSITY
140	6.0	13.5
120	7.6	7.5
115	9.6	6.1
105	12.0	4.1
90	13.4	3.0
70	14.8	2.5
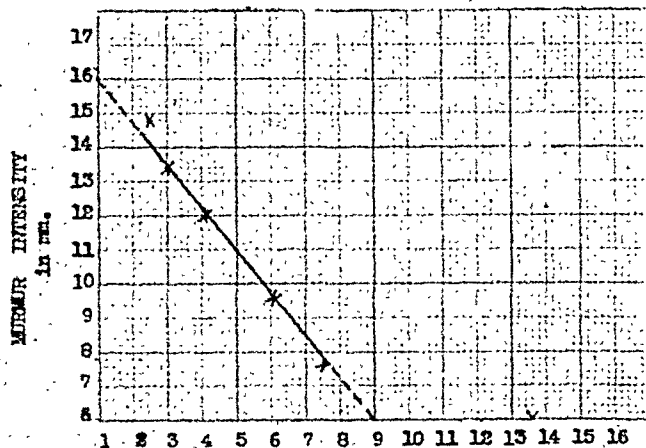
Fig. 3.—A graph of murmur intensity compared to blood viscosity. The dotted line represents the theoretical extension of the graph.
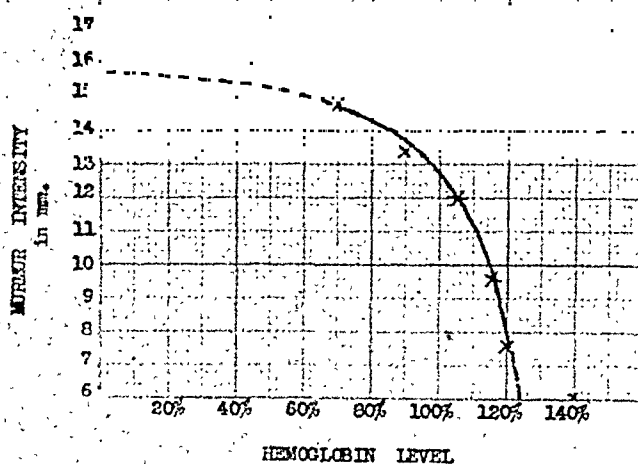
Fig. 4.—A graph of murmur intensity compared to blood hemoglobin content. The dotted line represents the theoretical extension of the graph.

DISCUSSION

Observers agree that murmurs are produced by turbulent blood flow. Hydraulic studies have shown that turbulence decreases with increased viscosity.[2] Since turbulence is the cause of murmurs, one would expect murmur intensity to decrease with increased viscosity. Fig. 3 presents evidence in support of this concept. Although some workers are of the opinion that, below 100 per cent hemoglobin, viscosity is directly related

to the hemoglobin and erythrocyte content,[2] all agree that, at hemoglobin levels over 100 per cent, the relationship of viscosity to hemoglobin is hyperbolic.[3, 4] Since viscosity increases hyperbolically with increased hemoglobin and erythrocyte count, the murmur intensity should drop precipitously with increasing blood hemoglobin levels. Fig. 4 shows that the experimental observations accord with this theory.

Although, for convenience, hemoglobin levels are given in this paper, it should be emphasized that the erythrocyte count is probably more important in determining viscosity. However, since the blood used in this experiment had a color index of one, the use of hemoglobin content is valid.

From Fig. 4, it may be deduced that a murmur heard at 100 per cent hemoglobin should have an amplitude of 13 mm. A murmur heard at 70 per cent hemoglobin measures 14.8 millimeter. The difference is 1.8 millimeter. A murmur 1.8 mm. above the zero point, or 7.8 mm., is slightly louder than the murmur recorded at 120 per cent hemoglobin. The latter is an unmistakable murmur, approximately as loud as the normal first heart sound (Fig. 2). This would indicate that a lowering of blood viscosity is, in itself, enough to bring out a definite murmur, even if the rate of flow and the size of the orifices are constant.

The intensity of the murmur decreased precipitously as the hemoglobin rose over 100 per cent (Fig. 4). At 105 per cent hemoglobin the murmur was louder than normal heart sounds (Fig. 2). At 120 per cent hemoglobin, it became much fainter, and, at 140 per cent hemoglobin, it disappeared completely. Since in both primary and secondary polycythemia erythrocyte counts over 7 million, hemoglobin levels from 125 per cent to 165 per cent, and viscosities of 20 to 32 are expected,[5] it follows that the absence of a murmur in polycythemia does not rule out gross structural cardiac abnormalities. Furthermore, the presence of a murmur in polycythemia probably indicates a much more extensive abnormality than it would if the blood picture were normal.

SUMMARY

1. A method of producing and recording a murmur is described.

2. The murmur produced was found to decrease precipitously with increased blood hemoglobin levels.

3. The results show that lowering of viscosity is, in itself, enough to produce a definite murmur where none was heard before. This may indicate the origin of the hemic murmur.

4. With high blood viscosities, the absence of a murmur does not rule out gross structural cardiac abnormalities.

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ELECTROCARDIOGRAPHIC STUDIES IN NEURO-CIRCULATORY ASTHENIA

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NEUROCIRCULATORY asthenia is not uncommonly confused with organic heart disease. In many instances, this is due to misinterpretation of changes in the electrocardiogram and a failure to recognize that the electrocardiogram may be altered at times by this condition. It is important to recognize the true nature of neurocirculatory asthenia to avoid a false diagnosis of organic heart disease and the possibility of engendering cardiac invalidism.

There are conflicting statements in the literature regarding the electrocardiographic findings in neurocirculatory asthenia. A recent editorial[1] states that the electrocardiogram in this condition does not reveal any structural change. Master[2] commented on the slender, asthenic person with a low diaphragm and small heart, and stated that, in a series of thirty cases which he observed, the electrocardiogram was typical. There were small QRS complexes in Lead I and tall QRS complexes in Leads II and III, with an occasional tendency to right axis deviation.

Craig and White[3] reviewed the electrocardiograms of 35 patients with neurocirculatory asthenia. There were 15 instances of sinoauricular tachycardia, 1 instance of auricular premature contractions with bigeminy, 8 instances of diphasic T waves in Lead II, with inverted T waves in Lead III, 6 instances of left axis deviation in obese patients, and 5 instances of a tendency to right axis deviation. In 5 patients there was a history of paroxysmal tachycardia. Graybiel and White[4] reported 7 cases of neurocirculatory asthenia with inversion of the T waves in Leads II and III.

Dry[5] lists the electrocardiographic changes which may occur in neurocirculatory asthenia as follows:

1. Prolonged P-R interval.

2. Prolonged QRS interval. usually with a shortened P-R interval.

3. Sinoauricular block.

4. T-wave changes which affect Leads II and III, or all three standard leads.

Other authors[6] mention elevation of the R-T segments in one or more leads and high voltage of the T wave in Lead I.

It is clear from the literature that there is no characteristic electrocardiogram in neurocirculatory asthenia.

Among 4,500 patients in the Cardiovascular Section of Lawson General Hospital over a period of two years, there were 150 patients with neurocirculatory asthenia with symptoms severe enough to warrant their seeking medical advice. Numerous other patients with mild symptoms of this condition were seen in routine consultation, but were omitted from this study. A review of the electrocardiograms taken on these patients showed that 49 per cent of them had variations from the textbook normal. The observations in our series of patients are tabulated in Table I.

It is to be noted that the most frequent abnormality was low voltage of less than 1 mm. of the T wave in Lead I, using 1 mm. as the upper limits of normal (Fig. 1, A). This occurred in twenty-two, or 14 per cent, of the cases.

A.	B.	C.	D.

| Low T₁ | Inverted T₂, T₃ | Before Tilting. | After Tilting. |
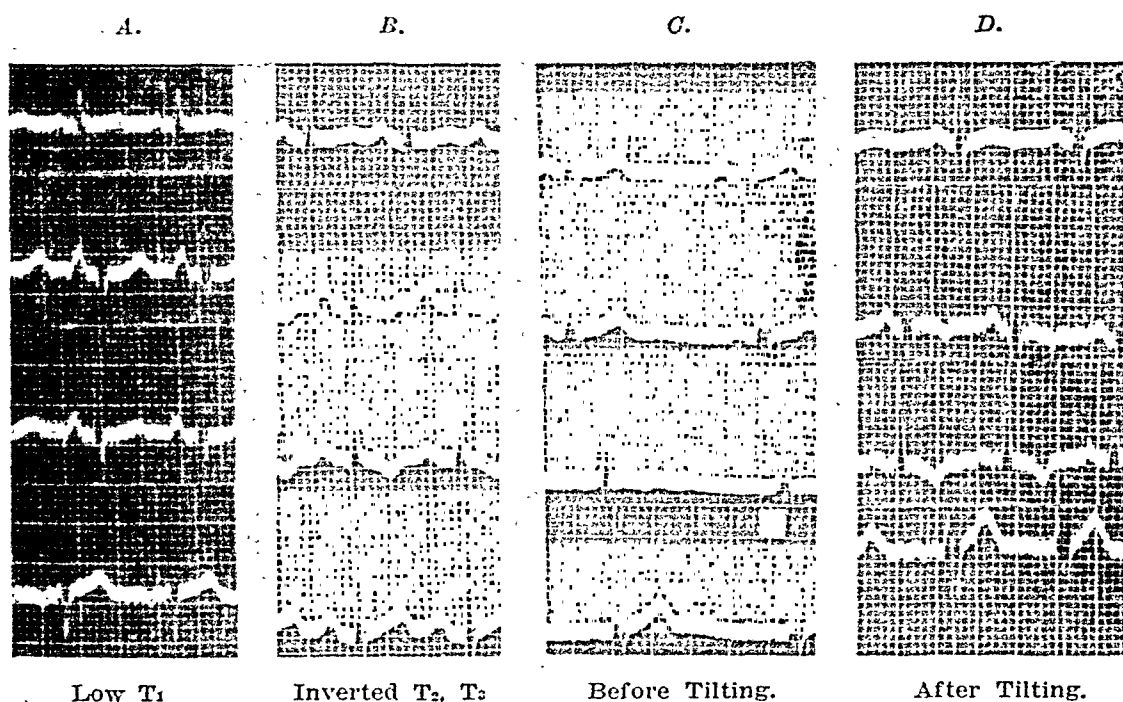
Fig. 1.

There were 6 additional instances in which both T_1 and T_2 were of low voltage. In only 2 instances was the T wave inverted in Lead I. Thus the T wave in Lead I was abnormal in 28, or 20 per cent, of the cases. This was usually accompanied by tachycardia.

There were 18 instances in which the T wave in Lead III was diphasic or inverted, and 9 instances in whch the T waves were inverted in Leads II and III (see Fig. 1, B). Thus the T wave was abnormal in Lead III in 27 instances, or 18 per cent of the cases.

The T wave was of low voltage in Lead II in 5 cases and diphasic or inverted in 9 cases, or abnormal in 21, or 14 per cent of the cases.

The P-R interval was prolonged in 7 instances in which there was no evidence of heart disease or history of any disease which might reasonably be associated with prolonged conduction. Atropine in doses of 1/75 grain was given intravenously to four men in this group. In

TABLE I

ABNORMALITIES OF THE ELECTROCARDIOGRAM IN SEVENTY-FOUR CASES OF
NEUROCIRCULATORY ASTHENIA

ABNORMALITY	FREQUENCY
Axis deviation, left	14
Axis deviation, right	6
Extrasystoles	6
Intraventricular block, S-wave type	1
P-R interval prolonged	7
Q_3 deep	3
R_4 small	1
QRS slurred all leads	4
S-T elevation	3
S-T depression	1
T_1 inverted	2
T_1 low	22
T_1 and T_2 low	6
T_2 diphasic and inverted	1
T_2 low	5
T_2 and T_3 diphasic and inverted	9
T_2 and T_3 inverted after tilting	12
T_3 diphasic and inverted	18
T_4 inverted	2
T_4 low	2
Low QRS_1, high $QRS_{2\ and\ 3}$	35

three cases the P-R interval returned to normal. It was felt that, when there was a response to atropine, prolongation of the P-R interval was due to increased vagal tone.

Extrasystoles were surprisingly infrequent; they were seen in only 6 cases. This is not a true picture, for they are much more common upon physical examination, in our experience, and there is considerable fortuitousness in the recording of these variations.

The type of change described by Master, consisting of a low amplitude of QRS in Lead I with a high amplitude of the QRS in Leads II and III, was seen in thirty-five instances, or 23 per cent of the cases. This variation is related to body build, and is associated with a long, narrow chest and low diaphragm with small heart. In our experience, these changes are not uncommon with this type of physiologic build, and are not believed to be related to the syndrome of neurocirculatory asthenia per se.

There were 12 additional patients whose electrocardiograms were normal in the recumbent position, but who developed inversion of the T waves in Leads II and III upon tilting to 65° on a tilt table (Fig. 1, C and D). The mechanism of this change is not clear, but it may be associated with a diminished venous return to the heart, with a secondary fall in cardiac output in patients with vasomotor instability. Hyperventilation may at times play a part, as has been pointed out by Thompson,[7] but this condition was not prominent in the present group of cases. These occurred in a series of 50 tilt table tests, with tracings taken immediately before tilting, three minutes after tilting, and twenty minutes after tilting. There were three positive tests, with in-

version of the T waves in Leads II and III in the absence of the clinical picture of neurocirculatory asthenia. Of these, there were two cases of angina pectoris and one of vasomotor instability without subjective symptoms.

There were 20 instances of axis deviation, including 14 cases of left axis deviation and 6 cases of right axis deviation. A tendency to right axis deviation was not uncommon. Other changes were intraventricular heart block of the S-wave type, deep Q_3, small R_4, S-T elevation or depression, and a T wave of low voltage or inverted in Lead CF_4.

The occurrence of alterations of the T waves, including low amplitude of the T wave in Lead I, and low amplitude and inversion of the T waves in Leads II and III, necessitates the differentiation of neurocirculatory asthenia from coronary arteriosclerosis with or without angina pectoris. The differential diagnosis rests upon the history and physical examination, and not upon the electrocardiographic findings. Similar changes may be observed in the electrocardiogram in neurocirculatory asthenia and in coronary arteriosclerosis.

From a brief review of the literature and from the results of this study, it is felt that there is no characteristic electrocardiogram in neurocirculatory asthenia. A number of variations from the normal may be encountered.

SUMMARY

The electrocardiographic variations in 150 patients with neurocirculatory asthenia are presented. A brief review of the literature concerning the electrocardiographic changes in neurocirculatory asthenia is given. The importance of avoiding misinterpretation of confusing electrocardiographic changes as evidence of organic heart disease is emphasized. Alterations in the electrocardiogram similar to those observed in coronary arteriosclerosis may be seen in neurocirculatory asthenia. The differentiation rests upon the history and physical examination, rather than upon the electrocardiogram. There appears to be no characteristic electrocardiogram in neurocirculatory asthenia.

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RUPTURE OF MITRAL CHORDAE TENDINEAE

Clinical and Pathologic Observations on Seven Cases in Which There Was No Bacterial Endocarditis

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MOST of the attention given to rupture of the chordae tendineae of the mitral valve has been accorded those instances which occur during the course of acute or subacute bacterial endocarditis, or which result from severe external violence to the chest. Frew[1] described a case in which rupture of the mitral chordae tendineae took place during a prolonged attack of acute rheumatic fever; and Frothingham and Hass[2] have reported an instance of spontaneous rupture of mitral chordae which were apparently not the site of previous disease.

In the last 2,400 autopsies at the Peter Bent Brigham Hospital, there were eleven instances of rupture of the mitral chordae tendineae. Four were associated with bacterial endocarditis involving this valve. The other seven patients presented no evidence of bacterial endocarditis and no history of severe trauma to the chest, but the mitral valves and their chordae tendineae showed scarring, calcification, or other pathologic changes. It is the purpose of the present report to discuss these instances of spontaneous rupture of scarred or chronically injured mitral chordae tendineae and to correlate the clinical and pathologic characteristics of the syndrome.

REPORT OF CASES

Case 1.—A 51-year-old white woman was first admitted to the hospital in February, 1941, because of shortness of breath of sudden onset three weeks previously. There was no history of rheumatic fever. Ten years before admission the patient was told that she had hypertension, but there had been no symptoms referable to the cardiovascular system. For over three years preceding admission she had been examined by her physician at intervals of two to three months. The systolic pressure had been consistently in the neighborhood of 260 mm. Hg. No cardiac murmurs had been heard. Three weeks prior to admission, after cleaning the cellar, tending the furnace, and lifting and shoveling coal, she climbed the stairs to her kitchen and thereupon became aware of severe, unusual shortness of breath. This subsided after a few minutes. On the following day she went to her doctor. Having examined her heart a month before and found no murmurs, he was

surprised on this occasion to hear a very loud systolic murmur all over the precordium. The patient was treated with rest and digitalis. Three weeks later she was admitted to the hospital.

Physical examination showed a markedly obese woman who was able to lie flat without distress. The pupils reacted to light. The arteries of the fundus oculi showed thickening and arteriovenous nicking, with several areas of old exudate. The neck veins were not distended. There was moderate, soft enlargement of the thyroid. The heart was enlarged to the left and a strong impulse was noted. No thrill was felt on this admission. There was a harsh, precordial, systolic murmur transmitted into the neck and left axilla, but no diastolic murmur was heard. The rhythm was normal, with a rate of 100 per minute. The blood pressure measured 220/130. The lungs were normal on auscultation. There was slight tenderness below the right costal margin, but the liver could not be felt. No edema was present.

Fig. 1.—Case 1. The atrial surface of the mitral valve. The cusps of the valve were thickened, but there was no significant degree of stenosis. There was considerable ballooning upward of the posterior cusp, from which the ends of two ruptured chordae tendineae projected into the valve orifice. Note the bulbous tips of the free ends of the ruptured chordae tendineae.

The blood Wassermann and Hinton reactions were negative. The vital capacity was 1,400 c.c., and the decholin circulation time was 17 seconds. The electrocardiogram showed left axis deviation. The patient was running a low-grade fever, which was ascribed to her urinary tract infection. This responded to sulfathiazole therapy, and she was discharged, afebrile and asymptomatic, on the thirteenth hospital day.

For eight months she felt fairly well on limited activity. Three weeks before her second hospital admission she exerted herself more than usual, and thereafter developed weakness, dyspnea, and orthopnea. Four days before admission, swelling of the feet and ankles appeared for the first time. She was readmitted to the hospital Nov. 4, 1941.

Physical examination showed a severely ill, perspiring woman, sitting up in bed and gasping for breath. The neck veins were distended up to the mandibles when the patient was in a sitting position. The heart was enlarged to the left. The rhythm was normal, except for occasional dropped beats, at a rate of 120 per minute. At the base a rough, loud systolic murmur was heard. At the apex and extending upward over the precordium, there was an intense systolic thrill and a very loud, blowing, systolic murmur. No diastolic murmurs were heard. The blood pressure was 225/115. There were moist râles throughout both lungs, with signs of fluid up to the fifth rib on the left and the seventh rib on the right. Liver dullness extended three fingerbreadths below the costal margin. There was well-marked edema of the legs. The electrocardiogram was essentially unchanged. A teleoroentgenogram showed only 10 per cent enlargement by height-weight ratio. The aorta was moderately tortuous and the hilar vessels were considerably engorged. There was fluid in both pleural sacs. There was definite dilatation of the left atrium posteriorly, with marked systolic expansion of the atrium, suggesting mitral regurgitation. She was given digitalis and diuretics, and was discharged much improved after nineteen days.

After discharge, the patient did fairly well on limited activity, except for several brief attacks of abdominal pain, distention, and vomiting. With the last of these, on May 31, 1942, she developed circulatory collapse, and was brought to the hospital. She died a few hours after admission.

Necropsy.—Anatomic Diagnoses: Rupture of chordae tendineae of mitral valve; fibrosis of mitral valve; cardiac hypertrophy and dilatation; generalized arteriosclerosis; hydrothorax, bilateral; ascites; passive congestion of viscera; aspiration of gastric contents in lung; multiple adenomata of thyroid; chronic cholecystitis; cholelithiasis.

The heart weighed 520 grams. The left atrium was considerably dilated, and the right atrium and ventricle somewhat less so; the left ventricle was dilated very little. The right ventricular myocardium measured 0.9 cm. in thickness, and that of the left ventricle, 2.2 centimeters. It was deep red in color and no areas of scarring were found. The tricuspid, pulmonary, and aortic valves were normal in size and texture. A few thrombi were found on the surface of the endocardium just beneath the aortic valve, but elsewhere the endocardium was smooth.

As seen from the atrial surface, the mitral valve was thickened and irregular, but there was no significant degree of stenosis. The ends of two ruptured chordae tendineae projected into the valve orifice from the posterior cusp (Fig. 1). The right portion of the posterior cusp was displaced upward into the atrium. The ruptured chordae were thickened and had rounded free ends. On a papillary muscle of the right group there were two rubbery, rounded elevations, each 2 mm. in height. These represented the original attachments of the ruptured chordae; the rupture had occurred just above the site of attachment. There was considerable atrophy of this papillary muscle, but the other papillary muscles were normal.

There was a moderate degree of sclerosis of the coronary arteries, but they were not occluded or thrombosed. The pericardial sac was normal.

Microscopic Examination.—There was a large amount of dense, hyaline, fibrous tissue in the mitral valve, especially in the central portions of the cusp. Small and large blood vessels were found in all parts

of the mitral cusps. No Aschoff bodies were seen. The stumps of the ruptured chordae tapered at their free ends, and the surfaces were everywhere covered by endothelium. Within the ruptured chordae, the tissue was dense and hyaline, with few cells and blood vessels. The papillary muscle at the point of attachment of the ruptured chordae showed considerable scarring (Fig. 2).

There was edema of the interstitial connective tissue of the myocardium. The myocardium was not otherwise remarkable.
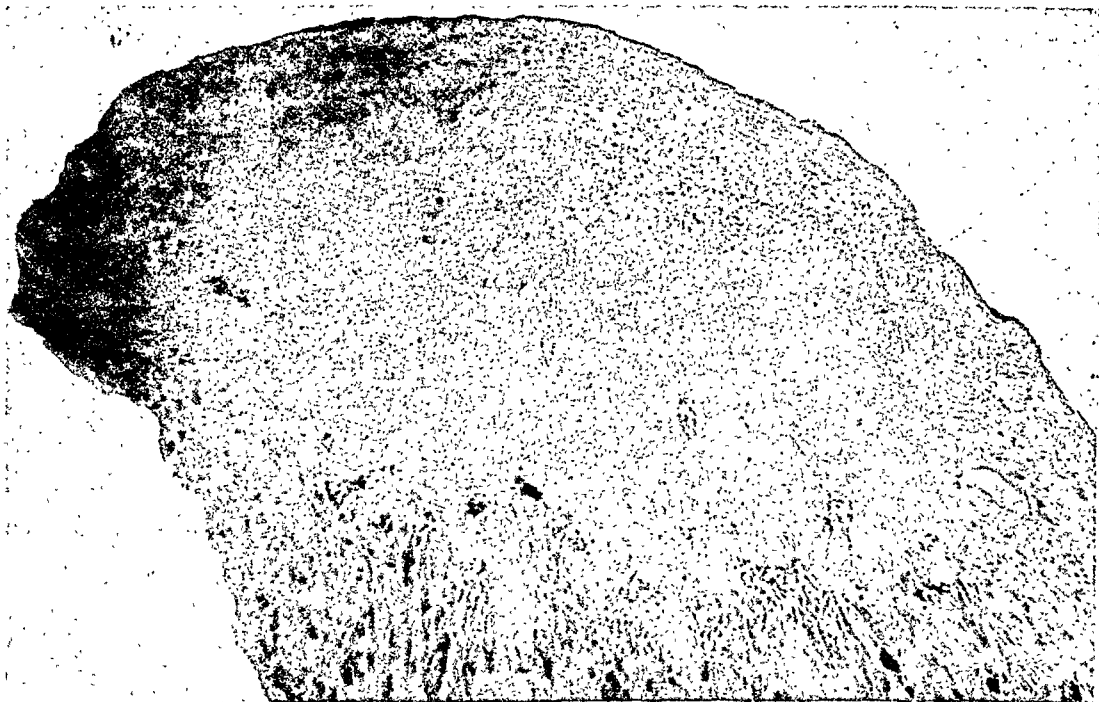
Fig. 2.—Case 1. Photomicrograph of the stump of a ruptured chorda tendinea attached to a papillary muscle. Hematoxylin and eosin stain; magnification, ×75 reduced.

CASE 2.—A 52-year-old white man was admitted to the hospital March 30, 1940. He gave no history suggesting rheumatic fever. Physical examination twenty-five years before was said to have been negative. Sixteen years before admission, during an exhausting struggle in quicksand, he experienced a severe, pressing pain over the heart. For one or two years before admission he had had a similar pressing pain to the left of the sternum on hurrying, particularly in a cold wind. For about three years there had also been shortness of breath on inclines or when running, and palpitation at various times. On the night before admission, the patient was awakened from sleep by a pressing pain in the left side of the chest anteriorly. He was extremely breathless on awakening, and this persisted until he found partial relief by sitting up. On the next day he was admitted to the hospital.

Physical examination showed an obese man, propped up in bed, breathless, weak, pale, moderately cyanotic, perspiring, and cool over the extremities. The temperature was 102° F. (rectal), the pulse rate, 140 per minute, and the respirations, 36 per minute. The heart was enlarged to the left and to the right. There was a diffuse apex impulse, but the radial pulse was noted to be small. On this and all subsequent examinations a coarse, loud, systolic murmur was heard over the precordium, maximal at the apex and along the left border of the sternum; this was accompanied by a systolic thrill. On the first exam-

ination, and irregularly thereafter, a low-pitched diastolic murmur was heard at the apex. The apical first sound was loud and snapping, and the pulmonary second sound was markedly accentuated. The rhythm was normal and the blood pressure was 100/80. Examination of the lungs showed moist inspiratory râles at both bases, inspiratory râles at the left apex, and râles in both phases of respiration at the right· apex. The abdomen was moderately distended; the liver was not palpable. The peripheral arteries were in good condition. There was no edema.

The blood Hinton and Wassermann reactions were negative. The electrocardiogram on admission showed sinus tachycardia, left axis deviation, occasional premature ventricular beats, and a normal Lead IV. Four subsequent electrocardiograms showed no essential change except for a digitalis effect. On May 8, the electrocardiogram showed auricular fibrillation. A roentgenogram on April 4 showed cardiac enlargement to the left and right, with a straight left border. There were coarse mottling of both lungs and partial consolidation of the right upper lobe. On April 9 the roentgenogram showed clearing of the lungs, revealing a fine, diffuse fibrosis in the right upper lobe. A third roentgenogram, on April 22, showed no essential change.

At first there was moderate symptomatic improvement. Scattered râles continued to be present over both lungs, particularly at the bases. Repeated examinations of the heart showed some variation in the intensity of the murmur and thrill. On several occasions systole was forcible enough to rock the chest, and there was a wide, lifting, apex impulse. At the same time the peripheral pulse was small. By the third week, signs of fluid appeared in both pleural sacs, more on the left; ascites developed; the liver was felt 3 cm. below the costal margin; the spleen was palpable and firm; and fullness of the neck veins was noted. On April 24 the venous pressure was 260 mm. of saline (normal, 100 mm.). The vital capacity diminished from 1,700 c.c. in the first week to 1,100 c.c. during the third week. On May 14, abdominal paracentesis yielded 1,200 c.c. of yellowish, cloudy fluid with a specific gravity of 1.010. By this time the edema had progressed to involve the lower portion of the body as far up as the nipple line. Auricular fibrillation developed on the fortieth hospital day and persisted until death. The patient became steadily weaker, developed incontinence of urine and feces, and died on the fifty-third hospital day.

Necropsy.—Anatomic Diagnoses: Rupture of chordae tendineae of mitral valve; fibrosis of mitral valve; myocardial fibrosis; cardiac hypertrophy and dilatation; passive congestion of viscera; thrombosis of branches of pulmonary arteries and veins; acute bronchopneumonia; hydrothorax, bilateral; ascites.

The heart weighed 470 grams. In situ, the heart was considerably dilated, especially the left atrium, and the left ventricle to an only slightly less degree. The cusps of the mitral valve were thickened, but there was no stenosis. The free edges were rolled, and numerous small, firm, white nodules were present on the atrial surface and along the annulus fibrosus of the anterior cusp. The chordae tendineae attached to the left papillary muscle and those extending from the right papillary muscle to the posterior cusp were thickened but intact. Eight chordae tendineae, which originally connected the anterior cusp and the right papillary muscle, were ruptured near the point of attachment to the papillary muscle (Fig. 3). Their free ends were tapered and rounded.

One ruptured chorda was approximately five times the thickness of the others. The portion of the right papillary muscle to which these chordae tendineae were originally attached was atrophic, in contrast to the other portion and the left papillary muscle, which were markedly hypertrophied and which deviated in the direction of the anterior cusp. The aortic, pulmonary, and tricuspid valves were normal. Small nodules similar to those on the mitral valve were present on the intima of the aorta near the orifices of the coronary arteries and on small areas of the endocardium of the right and left atria.

The myocardium was not remarkable. There was slight atheroma of the coronary arteries, but no occlusions were found. The pericardium was normal. Small Soldier's plaques were seen on the epicardium.

Fig. 3.—Case 2. The anterior cusp of the mitral valve was turned back. Eight chordae tendineae were ruptured, not all of which are shown in the photograph. Note the thickening of the chordae tendineae, the atrophy of the papillary muscle to which the ruptured chordae tendineae had originally been attached, and the hypertrophy of the papillary muscle with intact chordae tendineae.

Microscopic Examination.—The nodules described grossly were composed of dense, hyalinized, connective tissue covered by endothelium. The ruptured chordae were made up of dense, relatively acellular, connective tissue, with basophilic areas of degeneration. Endothelium covered the surface. There was dense connective tissue thickening of the mitral valve. A myocardial vein contained an organizing thrombus. There was a moderate increase in the connective tissue of the myocardium, but no Aschoff bodies or areas of infarction were encountered.

CASE 3.—A 54-year-old colored man was admitted to the hospital May 28, 1942. There was no history of rheumatic fever. Five or six

years before admission he had been told that he had high blood pressure, but his only complaint had been occasional attacks of mild epistaxis. Seventeen months before admission, while shoveling coal, he had a sudden attack of dyspnea which lasted for approximately forty-five minutes, during which time he was forced to sit still in an upright position. Thereafter, he had occasional, milder attacks which came on during the course of moderate exertion, but never at night. Usually he was able to discharge his duties without difficulty.

Seven months before admission he began to have a productive cough. Two months later he had the first of several attacks of sharp pain in the anterior part of the chest, apparently accompanied by dyspnea, which sometimes lasted over an hour. Gradually he developed troublesome shortness of breath on exertion, and, six weeks before admission, his physician prescribed a compound of squill, digitalis, and calomel, with moderate improvement. On the day before admission, while walking on the street, he became aware of increasing difficulty in breathing, profuse sweating, and a sensation of abdominal distention. This passed off after an hour, but he coughed up small quantities of bright red blood. On the following day there was a similar attack of dyspnea, because of which he was admitted to the hospital.

For approximately six months before admission he had been under the observation of a physician who had examined him on several occasions. Each time a loud systole murmur had been present. His doctor was under the impression that there had been no change in the character of this murmur.

Physical examination showed a lean, tired, orthopneic Negro, perspiring over the forehead. There were some narrowing of the arteries of the fundus and moderate arteriovenous nicking. A few hemorrhages were seen in the right eye ground, and some exudate in both. The peripheral arteries were thickened and tortuous. The blood pressure was 155/95; later it rose to 190/100. The neck veins were not distended. The heart was enlarged to the left. There were a heaving apical impulse and an apical systolic thrill. The rhythm was normal except for occasional extrasystoles. The rate was 100 per minute. There was a very loud, harsh, systolic murmur, maximal at the apex, but also heard over the precordium and posterior part of the chest. The lungs were normally resonant. There were moist râles at the bases of both lungs and over the upper portion of the right lung, posteriorly. The liver and spleen were not palpable. Slight edema of the ankles was present.

The blood Hinton and Wassermann reactions were negative. The decholin circulation time was fifteen seconds, and the venous pressure measured 40 mm. of saline. Roentgenograms showed marked cardiac enlargement, with a round, blunt left ventricle and a tortuous aorta. There was marked consolidation around the hila of both lungs, with complete consolidation of the right upper lobe. The electrocardiogram showed right bundle branch block.

While in the hospital there were numerous attacks of paroxysmal dyspnea and the chest became filled with râles. The patient failed steadily and died on the seventh hospital day.

Necropsy.—Anatomic Diagnoses: Rupture of chordae tendineae of mitral valve, old and recent; endocardial vegetations, organized; cardiac hypertrophy and dilatation; myocardial fibrosis; arteriosclerosis, generalized; pulmonary edema with hemorrhage; thrombosis of branches of pulmonary artery and vein from left lower lobe.

The heart weighed 860 grams. As studied in situ, the heart was very much enlarged, especially the left ventricle, which was larger than the three other chambers combined. As the mitral valve was viewed from above, the anterior cusp was found to be displaced upward (Fig. 4). The free ends of the ruptured chordae tendineae could be made out through the orifice. There were numerous small, grayish-white, soft masses on this cusp, as well as on the endocardium of the left ventricle and on the posterior leaflet of the aortic valve. All the ruptured chordae tendineae belonged to the group attached to the right papillary muscle, on which small nodules represented the ends of the ruptured chordae. There was moderate atrophy of this papillary muscle. The cusps of the mitral valve were thickened and their edges rolled, but there was no stenosis.

Fig. 4.—Case 3. The anterior cusp of the mitral valve was ballooned upward. The ruptured chordae tendineae are not shown in the photograph.

The left ventricular myocardium measured 3.2 cm. in greatest thickness; and the right, 1 centimeter. There were no areas of scarring. Moderate sclerosis was present in the coronary arteries, but no areas of occlusion or thrombosis were found. The pericardium and epicardium were not remarkable.

Microscopic Examination.—The ruptured chordae tendineae were composed of dense, hyaline, connective tissue, with basophilic degenera-

tion and a few areas of calcification (Fig. 5). Occasional mononuclear phagocytes and rare polymorphonuclear leucocytes were found near the free ends. The mitral valve was irregularly thickened because of increase in hyaline connective tissue, but there was little vascularization. On the surface there were several nodular excrescences composed of dense, collagenous tissue arranged in irregular lamellae. There was no inflammatory cellular infiltration. The masses noted grossly were platelet thrombi without organization; no bacteria were demonstrated.

Sections through the ends of the chordae tendineae attached to the papillary muscle showed two processes. One of these was the presence of very dense hyaline connective tissue, with small areas of calcification;

Fig. 5.—Case 2. The free end of a ruptured chorda tendinea. The surface was completely endothelialized, indicating that the rupture had taken place a long time before death. Numerous areas of calcification are shown. Eosin-methylene blue stain; magnification, X150 reduced.

this extended into the subjacent myocardium for a short distance (Fig. 6). The other process was characterized by the formation of fresh thrombi on the surface. There were a few mononuclear cells and polymorphonuclear leucocytes in these regions, and in and about some degenerating muscle fibers beneath the thrombi. There was a moderate increase in the interstitial connective tissue of the myocardium. No areas of infarction or Aschoff body formation were found.

In comment, the histologic observations indicated that the chordae tendineae had ruptured on two occasions: on one occasion, a long time before death, and, on the other, a few days before death. The thrombi were evidently formed at the time of, or after, the rupture of the second group of chordae tendineae. There was no evidence of bacterial endocarditis.

CASE 4.—A 78-year-old white farmer entered the hospital Feb. 6, 1938. He had had occasional attacks of tonsillitis, and, in his early twenties, had intermittent fever, requiring over four weeks' bed rest. At the age of 17 years he consulted a physician because of sharp, precordial, nonradiating pain of several weeks' duration. At this time he was told that he had heart disease. At the age of 50 years there was a recurrence of this pain, again of short duration.

Fig. 6.—Case 3. Fibrosis and calcification in a papillary muscle at the site of previous attachment of a ruptured chorda tendinea. Hematoxylin and eosin stain; magnification, ×150.

Fifteen years later he noted recurrence of sharp pain in the precordium and lower substernal region, this time upon exertion. For some years before admission he had noted weakness, easy fatigue, and intermittent swelling of the ankles. Two months before admission he fell, striking the anterior part of his chest. At about this time he began to be extremely short of breath on exertion, and developed persistent swelling of the ankles. A constant aching sensation appeared in the epigastrium associated with slight nausea. Four weeks before admission he consulted a physician, who prescribed digitalis.

Physical examination revealed a somewhat undernourished, elderly man with a malar flush. The temperature was 98.6° F., the pulse rate, 90 per minute, and the respirations, 26 per minute. The vessels

of the fundi showed slight changes in caliber. The radial pulses were equal, regular, and full; the dorsalis pedis pulsations were present. The heart was enlarged to both left and right. On admission the rhythm was normal; on subsequent examinations it was coupled. There were a rough, loud, precordial, systolic murmur, maximal at the apex, and a harsh mid-diastolic apical murmur. Both murmurs, which showed some variation in intensity, were accompanied by thrills. The blood pressure was 150/90. At the bases of both lungs there were numerous moist râles. A firm, tender, liver edge was felt two fingerbreadths below the right costal margin. The spleen was not palpable. There was moderate edema of the legs.
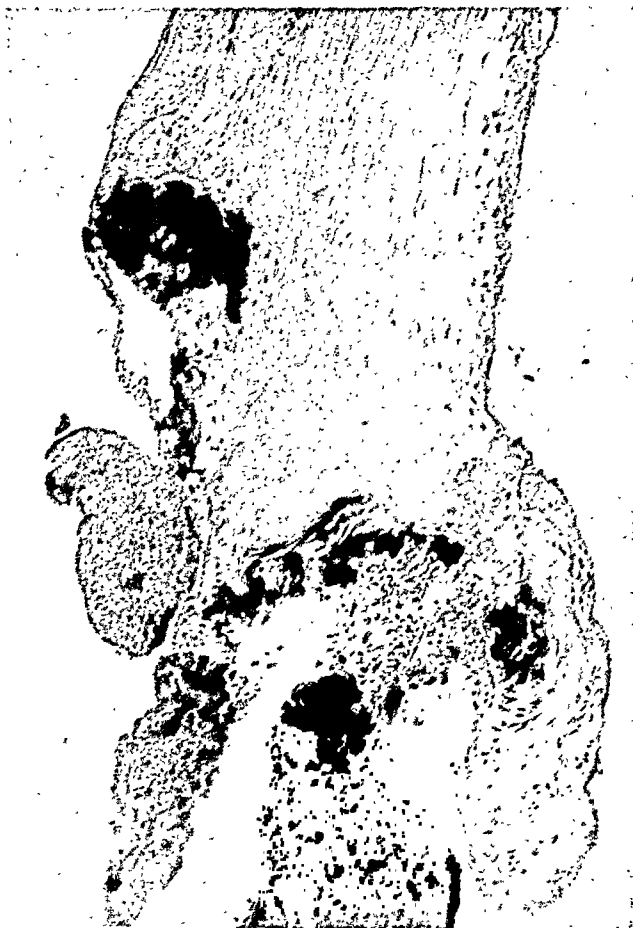
Fig. 7.—Case 4. Calcification in the free end of a ruptured chorda tendinea. Hematoxylin and eosin stain; magnification, X150 reduced.

The blood Hinton and Wassermann reactions were negative. The vital capacity was 1,800 cubic centimeters. The nonprotein nitrogen of the blood was 117 mg. per 100 c.c. on the sixth day. The electrocardiogram showed delayed A-V conduction and coupled beats.

The patient grew progressively worse, and death occurred on the eighth hospital day.

Necropsy.—Anatomic Diagnoses: Rupture of chordae tendineae of mitral valve; rheumatic heart disease; cardiac hypertrophy and dilatation; hydrothorax, right; passive congestion of viscera; edema, generalized; hyperplasia of prostate.

The heart weighed 420 grams. The mitral valve presented a firm nodular thickening of its free edges, especially on the posterior cusp. In the center of the anterior cusp there was an area of calcification measuring 1.5 by 0.5 cm.; another area of calcification, 1.5 by 1 cm., was located at the left lateral angle between the cusps; and a third, 2.5 by 1.5 cm., was present in the posterior cusp. The chordae tendineae were moderately thickened and shortened. Two chordae tendinae were ruptured, one belonging to the middle group of the posterior cusp and the other to the middle group of the anterior cusp. The papillary muscles of the left ventricle were hypertrophied. There was some thickening of the annulus fibrosus of the aortic valve, and fenestration was present along the free edge of its posterior leaflets. The other valves were not remarkable. The chambers of the heart were dilated to about the same degree. The firm, reddish-brown myocardium measured 1.6 cm. in thickness in the left ventricle, and 0.6 cm. in the right ventricle. There were no changes in the endocardium. Moderate sclerosis of the coronary arteries was present, most marked near their orifices.

Microscopic Examination.—The connective tissue of the mitral valve was somewhat increased in amount, and in some areas was more cellular than usual. There were no recent vegetations. The ruptured chordae were composed of very dense, hyalinized connective tissue, with areas of calcification and iron deposit. The free ends were rounded and covered by endothelium except for one point, where a deposit of calcium was covered by an unorganized thrombus (Fig. 7). The papillary muscles at the points of attachment of the ruptured chordae were extensively altered by increase in connective tissue. Near the stump of one of the ruptured chordae there was an area of calcification with a small amount of metaplastic bone formation. In the rest of the myocardium there were a few small areas of connective tissue proliferation, with loss of muscle cells. Most of it, however, was edematous but otherwise normal.

CASE 5.—A 71-year-old white garage man was admitted to the hospital Sept. 6, 1934. There was no history suggesting rheumatic fever. He had had chronic bronchitis for twenty years. For a year before admission there had been some shortness of breath on exertion, and for four to five months he had been frequently awakened by shortness of breath, forcing him to sit up. Some five months before admission he first noted swelling of the ankles. Pills, given by his physician, brought only moderate relief. For the last month there had been severe dyspnea, orthopnea, frequent attacks of paroxysmal dyspnea, and massive edema of the legs. He had had profuse sweating. In the few days preceding admission, he had been confused and drowsy.

Physical examination showed an obese elderly man with marked dyspnea, orthopnea, and cyanosis of the face and hands. The vessels of the fundi were obscured by opacities. There were moderate thickening and tortuosity of the peripheral vessels. The pulse was very small in volume, and the apex impulse could not be made out. The heart was enlarged to both left and right. The sounds were irregular and faint; there was a blowing systolic murmur, loudest at the apex of the heart, but also heard over the base, which varied in intensity on successive examinations from moderate to loud. The heart rate was 60 per minute, and the radial pulse rate was 30 per minute. The

blood pressure measured 180/90. At the base of the right lung there was flatness to percussion, with absent tactile fremitus and breath sounds. A few basal râles were heard. The abdomen was somewhat distended. Liver dullness extended 4 cm. below the right costal margin; the spleen was not palpable. There was massive edema over the ankles, legs, and sacrum.

The blood Hinton and Wassermann reactions were negative. The electrocardiogram showed left axis deviation, auricular fibrillation, and occasional ventricular extrasystoles.

The temperature on admission was normal, but in the following days it varied between 100° F. and 102° F. The heart rate ranged between 50 and 80 per minute. The patient failed rapidly, lapsed into coma, and died on the third hospital day.

Necropsy.—Anatomic Diagnoses: Rheumatic heart disease; mitral stenosis and insufficiency, rupture of chordae tendineae of mitral valve; cardiac hypertrophy and dilatation; hydrothorax, bilateral; edema of ankles; pulmonary thrombosis, recent; pulmonary emphysema.

The heart weighed 780 grams. The cusps of the mitral valve were fibrosed and calcified to such as extent that they formed a horizontal shelf with a slitlike orifice at the center which measured 1.5 by 0.7 centimeters. Although the annulus fibrosus measured 9 cm. in circumference, the orifice measured 5.3 centimeters. Three chordae tendineae of the anterior cusp were ruptured, and the free ends attached to the valve were 5 to 6 mm. in length. One of the ruptured chordae had a pointed end; the other two, bulbous tips. The portions attached to the papillary muscle were found in only one case; the fragment measured 3 mm. in length. The unruptured chordae tendineae varied from 1 to 1.5 cm. in length. Some were normal, but others were distinctly thickened. There were no bacterial vegetations. The papillary muscles were slightly hypertrophied. Slight puckering and adherence of the left anterior and the posterior leaflets were the only evidence of disease of the aortic valve. There was some dilatation of the tricuspid valve, but no fibrosis or alteration of the chordae tendineae. The pulmonic valve was normal.

There was marked dilatation of all the chambers of the heart. The left atrium had a capacity of approximately 125 c.c., and the right considerably more. The endocardium was slightly thickened in the left ventricle and normal in the right. The left ventricular myocardium measured 1.6 to 1.8 cm. in thickness, the right, 0.5 to 0.7 centimeters. It was reddish-brown in color, with some grey patches. The coronary arteries showed numerous atheromatous patches without occlusion or thrombosis.

Microscopic Examination.—The mitral valve was greatly thickened as a result of an increase in connective tissue. In part, the connective tissue was cellular. but most of it was dense and hyalinized. There was extensive vascularization of the valve, but no recent vegetations were encountered. The ruptured chordae were not sectioned. The myocardial fibers were large. Occasional small areas of scarring were seen, but there were no Aschoff nodules or infarctions. The coronary arteries showed considerable atherosclerosis without occlusion. There was considerable fibrosis of the epicardium, with some lymphocytic infiltration. The endocardium was not remarkable.

Case 6.—A 48-year-old white man was admitted to the hospital April 24, 1931. There was no history of rheumatic fever. When he was in the hospital because of a ruptured appendix nine years previously the heart was normal. One year later he was told that he had a "leaking valve." In the two years before admission, shortness of breath on exertion appeared. Six months later he became aware of irregularity and rapid rate of the heart, which were at first intermittent and later constant. For four months there had been a productive cough, insomnia, orthopnea, and nocturia. Nevertheless, he continued to be active and to work until a week before admission, when dyspnea became marked.

On physical examination the patient was a well-nourished, middle-aged, alert white man who was sitting up in bed. His hair was damp, and there was marked perspiration on the forehead and in the axillae. Moderate cyanosis was present in the nail beds of the fingers and toes. The radial and dorsalis pedis pulses were equal. There was marked cardiac enlargement to left and right. The rhythm was totally irregular, with an apical rate of 129 per minute and a radial rate of 66 per minute. A loud systolic murmur was present over the precordium, and a slight systolic thrill was felt in the apical region. No diastolic murmur was heard. The blood pressure measured 134/86. There were slight dullness and a few râles at the bases of both lungs, more on the left. The edge of the liver was palpated 5 cm. below the right costal margin, but the spleen could not be felt. There was slight, nonpitting edema of the ankles.

The blood Hinton and Wassermann reactions were negative. Roentgenograms showed considerable cardiac enlargement, to both left and right, with the left ventricle prominent downward and to the left. In each costophrenic angle there was a small amount of fluid. The lungs were slightly congested. The electrocardiograms showed auricular fibrillation and left axis deviation.

On digitalization, fluid restriction, and diuresis with theocin, the patient improved. However, on the twenty-third hospital day the temperature, which had shown an occasional fluctuation up to 100° F., began to rise, and varied for the last five days between 102° F. and 104° F. The pulse rate slowly rose to 110 to 120 per minute, with a slight deficit. During this time, the respirations varied between 25 and 40 per minute. The leucocyte count rose to 20,000 per cubic millimeter. There were no changes in the pulmonary or cardiac signs. Gradually he became weaker, lapsed into coma, and died on the thirtieth hospital day.

Necropsy.—Anatomic Diagnoses: Rupture of chorda tendinea of mitral valve, old; fibrosis and calcification of mitral valve; cardiac hypertrophy and dilatation; pulmonary thrombosis, recent, bilateral; infarction of liver and kidney; chronic passive congestion of liver; arteriosclerosis, generalized; chronic cholecystitis; cholelithiasis.

The heart weighed 560 grams. On examining the mitral valve from above, the posterior cusp was found to balloon up toward the atrium. Both cusps were slightly but diffusely thickened, and there were a few calcified nodules at the base of the posterior cusp. The orifice, however, admitted three fingers readily. Further inspection from below showed that one of the chordae tendineae of the posterior cusp was ruptured. The portion attached to the cusp was shortened and thickened. The site of attachment to the papillary muscle was rep-

resented by a small fibrotic area without evidence of recent reaction. In addition, there was a fibrous cord between the inferior surface of the posterior cusp and the ruptured chorda tendinea. The unruptured chordae tendineae were thickened and somewhat lengthened. There was slight dilatation of the tricuspid valve, but the cusps were normal. The pulmonic and aortic valves were not remarkable.

All chambers of the heart were dilated. The left ventricular myocardium measured 2 to 2.5 cm. in thickness, the right, 0.3 to 0.4 centimeters. It was deep pinkish-brown in color and flabby in consistency. There was moderate coronary sclerosis without occlusion of any of the arteries. The pericardial sac was normal.

Microscopic Examination.—There were small areas of scarring in the myocardium about medium-sized arteries. Some edema and fatty infiltration of the myocardium were also present. No Aschoff nodules or regions of infarction were present. There was considerable atheroma of a large coronary artery. The epicardium and endocardium were not remarkable. The mitral valve and chordae tendineae were not sectioned.

CASE 7.—A 78-year-old white man was admitted to the hospital July 10, 1930. He had had frequent nosebleeds as a boy, and one attack of tonsillitis many years before. In 1924, he underwent prostatectomy for hyperplasia of the prostate. At that time a systolic murmur was heard over the precordium. The blood pressure measured 130/85. He was again admitted, in 1929, for treatment of a duodenal ulcer which had been diagnosed roentgenologically. In the preceding years he had four attacks of hematemesis following epigastric pain. Examination at that time showed a harsh, loud, systolic murmur over the whole anterior part of the chest, transmitted halfway down to the umbilicus. The apex impulse was not seen or felt. The blood pressure measured 116/76. After discharge, he did well until about ten weeks before admission, when he began to experience considerable dyspnea on exertion, was forced to sleep propped up in bed, and developed a productive cough. Eight weeks before admission he began to sleep sitting up in a chair, and developed edema of the ankles which extended up the legs, at times even involving the lower part of the thighs. The attacks of dizziness and palpitation which he had had for years became more severe. Occasionally the patient experienced some pain in the chest.

Physical examination showed a fairly well-preserved, but confused, elderly white man in considerable respiratory distress. There were a malar flush and moderate cyanosis of the face, lips, tongue, and nail beds. The arteries of the fundus oculi showed slight arteriovenous nicking and diminution in caliber. There were considerable tortuosity and thickening of the peripheral vessels. A diffuse apex impulse was visible and palpable 11 cm. to the left of the midsternal line in the fifth intercostal space. There was a systolic thrill at the apex and in the third and fourth intercostal spaces. The heart sounds were of fair quality. The rhythm was normal. A loud, high-pitched, rather harsh, systolic murmur was heard all over the precordium, but loudest at the apex. No diastolic murmur was heard. The blood pressure measured 140/100. Moist and crackling râles were present at the bases of both lungs posteriorly up to the inferior angles of the scapulae. The liver and spleen were not palpable. There was considerable edema of the lower thirds of both legs.

The blood Wassermann and Hinton reactions were negative. The electrocardiograms showed left axis deviation.

While in the hospital the patient was restless and disoriented. The pulse rate rose steadily to 120 per minute. There was Cheyne-Stokes breathing, with periods of apnea lasting up to forty seconds. Incontinence of urine and feces developed, and, during the last two days, dark-red blood was passed by rectum. Death occurred on the eighth hospital day.

Necropsy.—Anatomic Diagnoses: Gastric ulcers, multiple; hemorrhage into gastrointestinal tract; bronchopneumonia; fibrinous pleuritis, right; anomaly of mitral valve; rupture of chordae tendineae of mitral valve; arteriosclerosis, generalized; chronic passive congestion of liver.

The heart weighed 450 grams. When the atrial surface of the mitral valve was inspected, the posterior cusp was found to bulge upward into the atrium. The orifice admitted three fingers. Both cusps were thickened and fibrosed, but not calcified. Inspection from below showed that all the chordae tendineae were shortened and thickened. Those of the anterior cusp were attached by a meshwork of fibers, not only along the margins of the cusp, but also for 2 cm. toward the annulus fibrosus. None was ruptured. The chordae tendineae of the posterior cusp were inserted by a similar network of interlacing fibers over the entire undersurface of the cusp. From this network the usual number of thick chordae tendineae extended to the papillary muscles. Three of the chordae tendineae of the posterior cusp were ruptured. The stumps of two of these were found on the papillary muscles. The papillary muscles were markedly hypertrophied. The only abnormality of the aortic valve was slight thickening and calcification of its free margins. The tricuspid valve was somewhat dilated; the pulmonic valve was normal.

There was dilatation of all the chambers of the heart, but predominantly of the left ventricle. The coronary arteries were tortuous, but showed minimal arteriosclerosis. The left ventricular myocardium measured 1.6 cm. in thickness, the right, 0.3 to 0.4 centimeters. It was pinkish-brown; no areas of scarring were found. The pericardium was not remarkable.

Microscopic Examination.—There were a few small areas of scarring about thickened arterioles of the myocardium, and a small amount of fat tissue was seen between some of the bundles. Elsewhere, the myocardial fibers were somewhat larger than normal, but otherwise were well preserved. The epicardium was not remarkable. The mitral valve and ruptured chordae tendineae were not sectioned.

DISCUSSION

Each of the seven patients discussed in this paper presented evidence of rupture of the mitral chordae tendineae. None had acute or subacute bacterial endocarditis. In each case disease of the valve and its chordae tendineae appeared to antedate the rupture.

The chordae tendineae of the left ventricle arise from two groups of papillary muscles, the medial, or posterior, and lateral, or anterior, and insert, respectively, in the posterior and anterior halves of the mitral valve cusps. They serve the function of checking the cusps during ventricular systole so that the valve closes efficiently under normal circumstances. Their rupture allows the affected portion of the cusp to balloon up into the atrium, leaving a gap through which blood regurgitates during systole.

It is difficult to state with assurance in most instances what was the nature of the disease of the mitral valve and its chordae tendineae antedating the rupture. In some, rheumatic fever was the antecedent disease. There was a history suggestive of rheumatic fever in Cases 4 and 7. At necropsy, the lesions in Cases 4 and 5 were those of rheumatic heart disease with involvement of the mitral valve and its chordae tendineae. In the other cases there was fibrosis of the mitral valve without stenosis. The chordae tendineae were thickened as the result of increase in connective tissue; this connective tissue occasionally showed degeneration, and, in Cases 3 and 4, calcium deposits. No sections of chordae tendineae were taken in Cases 5, 6, and 7. These lesions more nearly resembled quiescent rheumatic disease than any other type of involvement of these structures. However, there were no pathognomonic indications of rheumatic fever. The cause in these cases must, therefore, remain unknown. It is difficult to ascertain whether the curious anomaly of the mitral valve in Case 7 represented a congenital aberration or the organization of thrombi formed at the time of rupture of the chordae tendineae.

There was no difference in frequency of rupture of the chordae tendineae to either of the cusps in this series. In three cases (Cases 2, 3, and 5), the ruptured chordae tendineae were attached to the anterior cusp; in three (Cases 1, 6, and 7), to the posterior cusp; and in Case 4, one chorda tendinea of each cusp was ruptured. The point of rupture was nearer the papillary muscle than the free margin of the valve. In fact, the free ends attached to the valve were easily seen when the heart was opened, and were several millimeters in length, whereas prolonged search usually had to be made for the small nodules representing the ends attached to the papillary muscles. The number of ruptured chordae tendineae varied from one (Case 6) to very many (Case 3). In all instances except Case 6, more than one chorda tendinea was ruptured.

It has often been suggested that accidental cutting of chordae tendineae in opening the heart at necropsy has been confused with ante-mortem rupture by the pathologist. Especial care was taken in each of these cases to avoid this error. The ballooning of the cusp to which the ruptured chordae tendineae were attached was noted, and, in several instances, the free ends of the chordae tendineae were seen in the valve orifice before the ventricles were opened (Fig. 1). Furthermore, the bulbous enlargements of the ends of the ruptured chordae tendineae attached to the valves and the character of the portions on the papillary muscles leave no doubt as to the ante-mortem nature of the process. This was also verified by histologic examination in four cases; in the other three the hearts were preserved as gross specimens without microscopic study.

The stumps of the ruptured chordae tendineae were composed of mats of hyalinized and partially degenerated connective tissue, with a cover-

ing of endothelium (Figs. 2 and 6). The process of scarring extended for some distance into the subjacent myocardium, and calcification was occasionally found there. In Case 3 we regard the gross and microscopic appearances as indicating that chordae tendineae ruptured at two periods, separated by a long interval. This provided material for study of the tissue sequences consequent to rupture. At the time of rupture, thrombi form over the severed ends and there may be small hemorrhages in the surrounding tissues. As these become organized, the surfaces exposed to the blood stream are endothelialized. The calcification may have taken place in degenerated connective tissue, but it is also possible that it may have been deposited in areas of hemorrhage.

The papillary muscles to which the ruptured chordae tendineae had formerly been attached were atrophied in some instances and hypertrophied in others. If all the chordae tendineae attached to one of the cusps were ruptured (as in Case 3), the corresponding papillary muscle underwent atrophy. Under these circumstances there could be no tension on the papillary muscle at any period of the cardiac cycle, and the muscular tissue therefore became atrophied through disuse. On the other hand, the rupture of one or a few chordae tendineae led to hypertrophy of the papillary muscle if the rest of the chordae tendineae attached to that structure remained intact, because of the increased work imposed by the mitral regurgitation (Cases 4, 5, and 7). A confirmation of this interpretation was found in Case 2. Eight chordae tendineae attached to one portion of the anterior cusp were ruptured, but the rest of the chordae tendineae of this cusp were intact. The portion of the papillary muscle to which the 8 ruptured chordae tendineae had been attached had undergone atrophy, whereas the part with intact chordae tendineae showed very marked hypertrophy (Fig. 3). The fact that there were striking changes in the papillary muscle is a further indication that the rupture had taken place a considerable time before death.

The weight of the heart was increased in all patients. It varied from 420 grams to 860 grams, with an average of 580 grams. Since there were other severe cardiac lesions in some of the cases, this hypertrophy cannot be attributed to rupture of the chordae tendineae entirely. However, in the case of the patient with the largest heart (Case 3), the lesions other than rupture of chordae tendineae were minor. It appears, therefore, that rupture of chordae tendineae of the mitral valve, with the consequent mitral regurgitation, leads uniformly to a considerable degree of cardiac hypertrophy regardless of what other lesions may be present.

In all cases in this series, the heart as a whole was dilated. The relative degree of dilatation of the chambers varied from patient to patient. It is worth noting, in passing, that in Cases 5 and 6, there was rather marked dilatation of the tricuspid valve, and that the measurements of the tricuspid valve were at the upper limits of normal in the other cases.

In view of the pathologic changes which have just been discussed, it is possible to re-evaluate the relation of chest trauma and of violent exertion to rupture of the mitral chordae tendineae. It is clear that chordae which are on the verge of rupture might well break under such circumstances, just as, presumably, normal chordae break as the result of severe external violence. However, most of the patients in this series gave no such history. It therefore appears that exertion and trauma are not of primary causative importance in the rupture of diseased mitral chordae tendineae, but may occasionally determine the moment at which the break occurs.

The symptoms which appear after rupture of the mitral chordae are not specific for this condition. They are those of congestive heart failure, which may be abrupt or insidious in onset and progressive or remittent in its course. The history, however, is of the first importance if it can furnish satisfactory evidence that the typical murmur made a sudden appearance. This will usually consist of a reliable statement by a previous examiner that no murmurs were present at some time in the months or years immediately preceding the development of symptoms.

All seven patients had a loud, usually harsh or coarse, precordial systolic murmur, maximal in the region of the apex and left sternal border. In six cases this was accompanied by a thrill, also maximal in that area, or palpable only there. Three patients showed some variation in the intensity of the murmur, including the two who were under observation for the longest period. In these two the thrill was not present at all times. Two patients also had low-pitched apical diastolic murmurs. In one instance, Case 4, in which the murmur was accompanied by a diastolic thrill, there was a well-marked, firm thickening of the mitral cusps which might have accounted for the diastolic murmur. In the other, Case 2, the murmur was faint and irregularly heard. Here the cusps were moderately thickened, but there was no stenosis. The degree of fibrosis of the valve was approximately the same as in Cases 1, 3, 6, and 7, in which no diastolic murmurs could be heard. However, in Case 2, there was the unusually large number of eight ruptured chordae attached to the anterior cusp. It is possible that freely movable chordae on the valve cusps may, in some instances, contribute to the production of a diastolic murmur. Diastolic murmurs have been reported in four cases of rupture of a papillary muscle without disease of the mitral valve itself.[2-5] In two instances of rupture of a papillary muscle[1,2] in which adequate observations appear to have been made, no murmur was heard. It is conceivable that rupture of chordae tendineae might also fail to produce a murmur.

The heart was examined roentgenologically in four cases. In Cases 1 and 2, in neither of which was there a significant mitral stenosis at autopsy, moderate dilatation of the left atrium was observed roentgenologically. The left atrium in Case 1 exhibited a systolic pulsa-

tion. Dr. M. C. Sosman, in a personal communication, has noted this in two other patients who are still living. He feels that the sign is strongly suggestive of rupture of the mitral chordae tendineae. If further study confirms this, the observation will be of great assistance in the diagnosis of the condition. It is actually a sign of very brisk mitral regurgitation.

Electrocardiograms were taken in all instances. Five patients, including two with hypertension, presented left axis deviation. Three patients had auricular fibrillation, which in one instance developed during the hospital course.

An estimate of the interval between rupture of the chordae and the onset of clinically evident congestive heart failure is extremely difficult, but the evidence suggests that this interval may last a number of months and possibly even years. In the only instance (Case 1) in which rupture of the chordae could be dated definitely by the appearance of a murmur, nine months elapsed before the patient experienced outspoken symptoms of congestive failure, in spite of marked hypertension for at least the preceding ten years. In Case 6 the patient had been told he had a heart murmur eight years before his death, and for two years had had some dyspnea on exertion. In Case 7, the patient had a loud precordial systolic murmur six years before his final admission to the hospital. However, an anomalous insertion of chordae on the valve, rather than rupture of the chordae, may have accounted for the murmur during part of this time. In Case 2, the patient had had exertional dyspnea for three years before his hospital admission, and the autopsy observations indicated that rupture of the chordae tendineae had antedated by some time the appearance of definite and progressive congestive failure. It is, however, doubtful that it took place as long as sixteen years before, during his struggle in quicksand. The post-mortem examination in Case 3 showed that chordae had ruptured on at least two separate occasions, one shortly before death. The patient was known to have had a loud murmur at least six months before death, at a time when he was having only relatively mild symptoms. There is no satisfactory evidence to date the time of rupture in Cases 4 and 5. In no instance was it clear that rupture of the chordae produced any significant immediate symptoms. This was also the experience of Frew,[1] who reported rupture of the chordae in a child of eight years, and of von Albertini,[9] who described the case of a 63-year-old man whose rupture was evidently the result of violent chest trauma. Frothingham and Hass[2] dated the accident in their case from an attack of paroxysmal nocturnal dyspnea which was followed by progressive congestive failure lasting until death, eight months after the attack. It is, however, not at all uncommon for patients with long-standing valvular disease to develop sudden congestive failure from which they never recover.

The diagnosis of rupture of the chordae tendineae of the mitral valve should be entertained particularly in the case of a middle-aged or elderly person who has suddenly developed, without dramatic incident, a loud precordial systolic murmur, maximal at the apex and left sternal border, where it is usually accompanied by a thrill. An apical diastolic murmur may also be present. Congestive failure is not likely to make its appearance for months or even years after the onset of the murmur. Auricular fibrillation sometimes occurs. Roentgenograms may show enlargement, and even a systolic pulsation, of the left atrium.

The differential diagnosis includes bacterial endocarditis, rupture of other valves, rupture of a papillary muscle, and spontaneous perforation of an infarcted interventricular septum.

Bizarre murmurs sometimes occur during the course of bacterial endocarditis. As already stated, chordae may be ruptured as the result of an ulcerative process. The demonstration of organisms in the blood stream is, of course, usually possible.

Any valve may be ruptured by severe external violence.[10, 11] Spontaneous rupture or retroversion of a syphilitic aortic valve cusp may produce loud diastolic murmurs and thrills.[12] The location and character of the murmur, the evidences of free aortic regurgitation, and positive serologic reactions should easily differentiate this condition.

Quite a different course usually attends the spontaneous rupture of a papillary muscle from that which follows rupture of the mitral chordae tendineae. Rupture of a papillary muscle is likely to precipitate an immediate cardiac catastrophe. Twenty-five instances of this accident have been described in all, but only the seventeen reported since 1909 are suitable for analysis. Of these patients,[3, 4, 7,13-18] ten apparently died within twenty-four hours and six[5, 16, 19-22] within fifteen days. One lived for ten months.[6] Rupture of the muscle is usually marked by acute pulmonary edema and peripheral circulatory collapse, even syncope. This results from the circumstances under which the accident occurs. Spontaneous rupture of a papillary muscle is almost always occasioned by an acute myocardial infarct which has involved the particular muscle. The myocardial reserve is therefore slight, and the free mitral regurgitation caused by papillary rupture is an additional cardiac burden which is usually sufficient to produce severe and rapid heart failure.

Both rupture of a papillary muscle and perforation of the interventricular septum may give rise to cardiac signs similar to those produced by rupture of the chordae tendineae. There has been great variation in the murmurs reported in instances of rupture of a papillary muscle. In twelve reported cases in which an examination of the heart was recorded, there have been four instances with systolic murmurs,[16, 20-22] usually loud and maximal at the apex; one

with an apical diastolic murmur;[5] three with systolic and diastolic murmurs;[3, 5, 6] two in which no murmur could be heard;[7, 8] and two in which a murmur was heard, but not timed.[4, 18]   Sager[23] has described the signs of perforation of the interventricular septum as a precordial systolic murmur and thrill, usually maximal over the fourth and fifth intercostal spaces along the left sternal border, or over the lower part of the sternum.   Later observers have been in agreement with this.   Both accidents are almost always preceded by acute myocardial infarction.   The history and clinical and laboratory observations which are characteristic of infarction should in most instances serve to differentiate these conditions from that produced by rupture of the chordae tendineae.

Rupture of the mitral chordae tendineae thus occurs occasionally in the absence of bacterial endocarditis.   The condition can be diagnosed during life with a fair degree of accuracy.   Since there is a certain similarity in the progress of the disease, a correct diagnosis should make possible a more accurate prognosis.

SUMMARY

The histories and pathologic observations in seven cases of rupture of the mitral chordae tendineae are reviewed.   Patients with bacterial endocarditis were excluded from the series.   All showed fibrosis and chronic injury of the mitral valve.   In two, the lesions were those of rheumatic heart disease; in the remainder, the changes suggested quiescent rheumatic disease, but were not pathognomonic.

The chordae of the two valve cusps were ruptured with equal frequency in this series, and usually more than one was broken.   The point of rupture lay close to the papillary muscle.   The stumps consisted of hyalinized and partially degenerated connective tissue, with a covering of endothelium.   Scarring extended into the subjacent myocardium.   The corresponding papillary muscles underwent atrophy if all their chordae were broken, but showed hypertrophy if a number were left attached.   It was clear from inspection that rupture of the chordae must have allowed a high degree of mitral regurgitation. All hearts were dilated and hypertrophied, with an average weight of 580 grams.   The histories of the patients did not indicate that external violence or vigorous exertion were etiologic factors of primary importance in rupture of the mitral chordae tendineae.

The symptoms after rupture of the mitral chordae tendineae are those of congestive heart failure, which may be insidious or abrupt in its onset and progressive or remittent in its course.   Months or even years may elapse between rupture and the onset of frank congestive failure.

Rupture of the chordae is suggested by the sudden appearance of a loud precordial systolic murmur, maximal at the apex and left sternal border, where it is usually accompanied by a thrill.   An apical

diastolic murmur may also be present. Auricular fibrillation sometimes occurs. Roentgenograms show cardiac enlargement, and fluoroscopic examination may demonstrate systolic pulsation of the left atrium.

The differential diagnosis includes bacterial endocarditis, rupture of a valve cusp, rupture of a papillary muscle, and perforation of an infarcted interventricular septum.

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THE EFFECT ON THE BLOOD PRESSURE OF NORMAL PERSONS AND HYPERTENSIVE PATIENTS OF GLYCERYL TRINITRATE, SODIUM NITRITE, ERYTHROL TETRANITRATE, AND MANNITOL HEXANITRATE

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OUR knowledge of the relative action on blood pressure of nitroglycerin, sodium nitrite, erythrol tetranitrate, and mannitol hexanitrate* is taken largely from reports which appeared prior to 1913.[1-6] At present these drugs are widely used, and their efficacy and applicability deserve further study. In the experiments reported herewith, the four most commonly used "nitrite" drugs were administered in rotation to a number of patients, and the blood pressure effects observed. The results, in general, confirm the observations of the earlier workers.

METHOD

Normal persons and hypertensive patients in the Strong Memorial Hospital and Rochester Municipal Hospital (see Table I for details concerning the patients) were given the four drugs in rotation. The patients were led to believe that the blood pressure measurements were a part of their routine management. They were not removed from the divisions for the tests, and carried on slightly restricted but essentially normal activities.

The blood pressure of each subject was recorded at intervals of one minute during the control period of thirty minutes or less. Then a drug was given, and measurements were made at one-minute or two-minute intervals until the drug action was complete and the blood pressure had

TABLE I

DATA ON PATIENTS

	NORMAL	HYPERTENSIVE
Number	19	19
Sex: Males	10	12
Females	9	7
Age: Range	15-81	20-74
Average	35	51
Predrug pressure:		
Systolic	118±11	184±25
Diastolic	75±8	104±18

*Because of the chemical instability of mannitol hexanitrate, this compound was used in the form of Maxitate, a stabilized preparation furnished by the R. J. Strasenburgh Company, which contains lactose and starch as diluents.

become normal. Rest periods were permitted for the longer acting drugs. Examples of the records are shown in Fig. 1; the upper record is of a hypertensive patient, and the lower record is of a normal subject. Three observers made the blood pressure readings; each one used
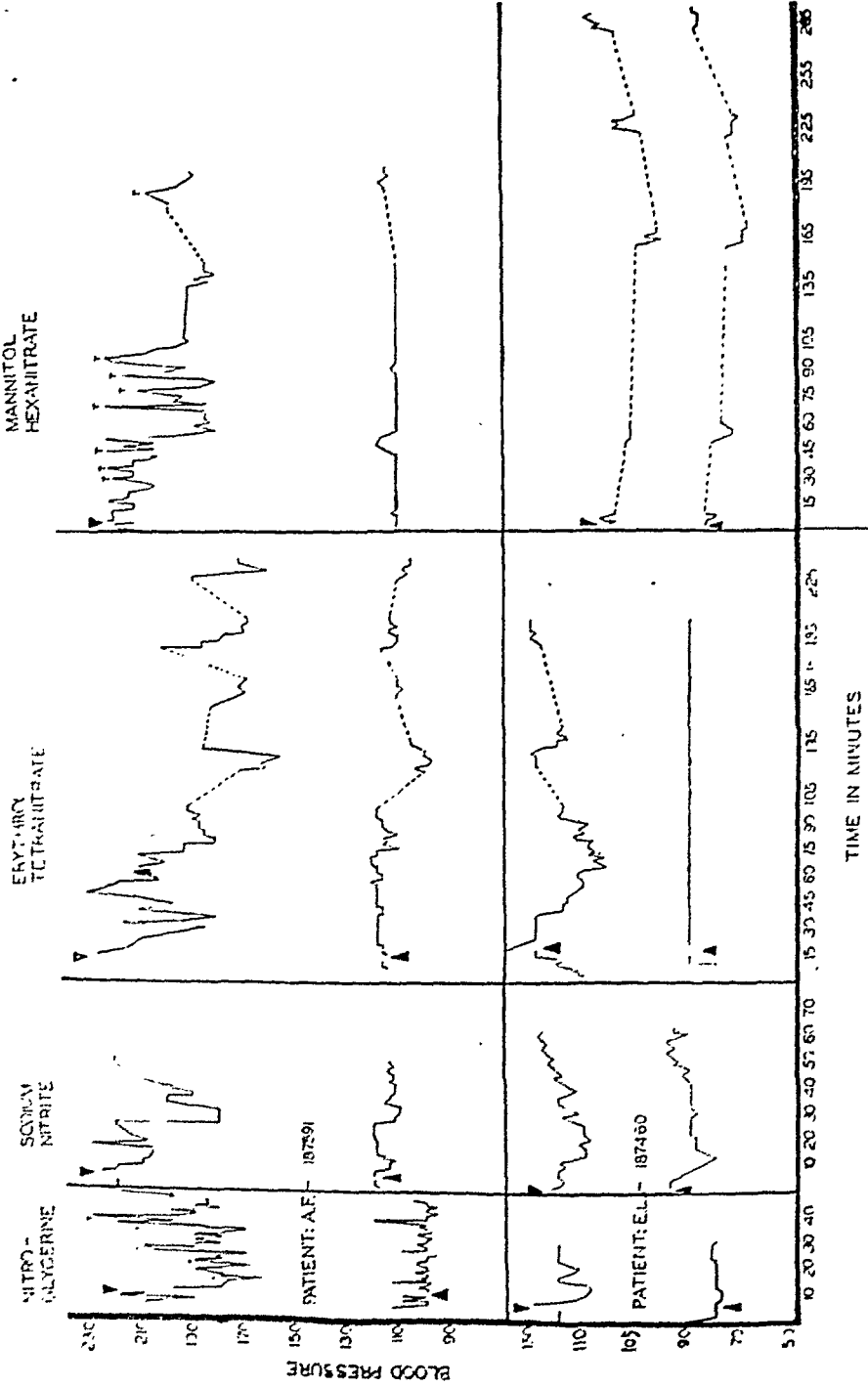
Fig. 1.—Sample blood pressure records. These charts illustrate the general plan of the experiment. Each of four drugs was given to the same patient (compare Tables III and IV). The records of two patients are shown: that of A. F., a hypertensive patient, shown above, shows marked emotional lability; talking (T) produced sharp momentary increases in systolic blood pressure; that of E. L., a normal person, shown below, gives a fairly good comparison of the amount and duration of decrease in blood pressure for each of the four drugs.

the method to which he was accustomed. All measurements were made on the same arm. A lowering of blood pressure was ascribed to the drug only when the pressure fell below the lowest readings in the control period.

The doses of the four drugs and the routes of administration were as follows: nitroglycerin, 0.006 Gm. sublingually and orally; sodium nitrite, 0.13 Gm. (sometimes 0.065 Gm.) orally; erythrol tetranitrate, 0.016 Gm. orally; and mannitol hexanitrate, 0.032 Gm. orally.

Amount of Fall in Blood Pressure.—Of the subjects who showed a well-sustained fall of blood pressure, not many had a very large decrease. Fig. 2 pictures the lowering of systolic pressure produced by each of the drugs. Each solid bar represents the average fall in systolic blood pressure following the drug specified. There was almost never a gradual decline or return of the blood pressure. Occasionally, there were isolated values 10 to 20 mm. lower than the general level of blood pressure during the period of drug effect. Such isolated occurrences should not be taken as an index of drug action. If relief of hypertension is to be of value, it should be sustained for sufficient time to relieve the myocardium of its burden. Therefore, average blood pressure for the period of drug effect was recorded throughout.
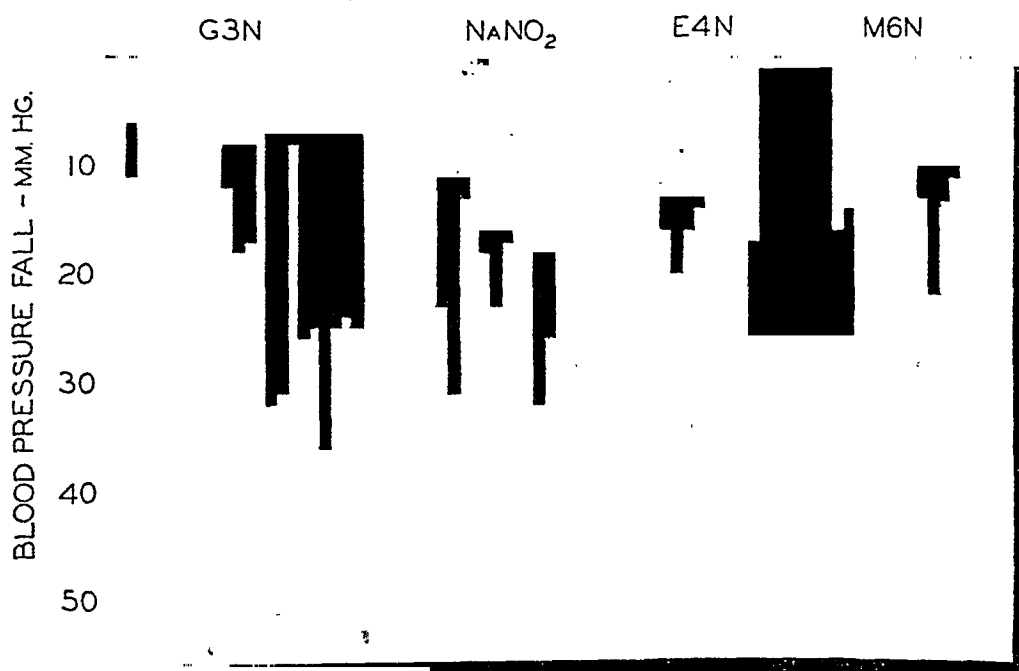
Fig. 2.—Fall in blood pressure produced by the four drugs. G3N = glyceryl trinitrate; NaNO₂ = sodium nitrite; E4N = erythrol tetranitrate; M6N = mannitol hexanitrate. Each solid bar represents the fall in blood pressure after the drug specified. Note that the average blood pressure lowering is of the same order for each drug.

From Fig. 2 it is seen that the greatest individual variation in the amount of blood pressure lowering occurred with nitroglycerin and sodium nitrite. Also, in isolated cases, the greatest actual amount of fall followed these two drugs. With erythrol tetranitrate and mannitol hexanitrate there was never a marked fall, but most of the subjects who responded gave fairly consistent responses. With each of the drugs the average fall in blood pressure was about the same (Table II); the statistical analysis of the data is given in the footnote to Table II. In

TABLE II

MEAN EFFECTS OF DRUGS ON BLOOD PRESSURE

	NORMAL				HYPERTENSIVE			
	NaNO₂	G3N	E4N	M6N	NaNO₂	G3N	E4N	M6N
Maximum drug effect (mm. Hg)	$-\frac{10}{5}$ (13)	$-\frac{11}{7}$ (14)	$-\frac{7}{5}$ (12)	$-\frac{7}{5}$ (12)	$-\frac{16}{7}$ (17)	$-\frac{21}{7}$ (17)	$-\frac{14}{5}$ (12)	$-\frac{12}{4}$ (16)
Drug effect commences (min.)	7	3	36	21	7	3	34	42
Drug effect ends (min.)	79	18	247	320	61	26	335	291

The standard deviations of each average blood pressure fall are as follows:

"S"	NaNO₂	G3N	E4N	M6N
Systolic	10	8	7	9
Diastolic	5	5	6	8

Parenthetical figures indicate the numbers of experiments yielding the figures averaged to obtain those given here.
G3N = glyceryl trinitrate.
E4N = erythrol tetranitrate.
M6N = mannitol hexanitrate.
The averages given above are to be compared with the "S" values; for example, the average blood pressure fall for G3N ± its standard deviation is 11±8. "S" values are calculated according to Fisher.

general, a patient who responds to one of these drugs will have an average fall in blood pressure of 10 to 20 mm. of mercury.

Time Required for Drug to Take Effect.—The average times before the onset of a fall in blood pressure after the administration of the drugs are shown in Table II. The time of onset is fairly constant for nitroglycerin and sodium nitrite, but varies widely for erythrol tetranitrate and mannitol hexanitrate. This variation may be ascribed to the slow absorption of the latter two drugs.

Duration of Blood Pressure Responses.—Table II also gives the average duration of the period of blood pressure decrease after each of the drugs. The duration of fall after nitroglycerin was surprisingly constant. For the other three drugs the durations varied widely. In order of duration of effect, nitroglycerin < sodium nitrite < mannitol hexanitrate = erythrol tetranitrate. However, this is an inadequate statement; the nitroglycerin effect was limited to about fifteen minutes, the sodium nitrite effect lasted about an hour, and erythrol tetranitrate and mannitol hexanitrate maintained an effect for about four hours on the average (see Tables III and IV).

Blood Pressure Stability and Lability.—The minute-by-minute fluctuation of blood pressure was surprising. Often, without apparent cause, the blood pressure of some subjects (normals as well as hypertensives) would vary 10 to 20 mm. Hg and return to its previous level, all in the space of two readings at one-minute intervals. No apparent change in the subject would be seen, nor would the pulse rate change. In other instances the pressure would remain constant within 5 mm. throughout the period. In some cases a considerable elevation occurred while the subject was talking or laughing. No relation between this type of phenomenon and response to a drug could be ascertained. One patient with quite a labile blood pressure is worthy of note. She (A. F., Fig. 1) had readings taken at one-minute intervals that fluctuated between 165/98 and 230/120, depending on whether she was quiet or talking and laughing. Her pulse rate varied between 76 and 92 per minute without concomitant changes in blood pressure.

Pulse Pressure.—Many subjects had a lowering of systolic pressure without any change in the diastolic; however, not a single subject had a fall of diastolic pressure as great as that of the systolic. When these drugs produced a fall of blood pressure, the effect was nearly always to reduce the pulse pressure.

Pulse Rate.—The pulse rate was counted between every three or four blood pressure readings. There was seldom any increase in pulse rate accompanying a fall of systolic pressure or decrease in pulse pressure.

Response to Drug.—Fig. 3 shows the number of subjects studied and the percentage who showed a blood pressure response to each of the

TABLE III

Data on Normal Persons

PATIENT	AGE (YR.)	G3N P	G3N ΔP$_{max}$	NaNO$_3$ P	NaNO$_3$ ΔP$_{max}$	E4N P	E4N ΔP$_{max}$	M6N P	M6N ΔP$_{max}$	BEG. G3N	BEG. NaNO$_3$	BEG. E4N	BEG. M6N	END G3N	END NaNO$_3$	END E4N	END M6N
BR	17	132/80	-16/0	126/81	-14/-4	126/83	-6/-6	124/80	-12/-3	2	5	63	38	22	19	523	489
DO	15	107/78	-8/-3	103/70	+4/+2	112/64	-8/-6	112/75	-18/-16	2	7	39	40	16	21	445	473
LA	65	140/83	-14/-2	151/98	-20/-16	143/84	-8/0	121/82	-18/-12	2	4	56	46	17	54	92	252
CI	16	107/68	-4/0	104/67	0/0	112/67	0/0	104/68	-2/-2	4			60	7			306
GR	38	118/70	-6/+10	111/74	-2/+2	121/77	-6/+6	120/74	-8/+4	6	12	50	128	17	30	246	304
GA	33	120/73	-12/0	121/68	-20/-3	121/61	-14/+8	118/61	-22/-8	1	9	27	22	13	344	370	306
FO	56	112/77	-10/-3	112/73	-10/+4	120/90	0/0	114/80	0/0	2	5			14	29		
AS	81	118/75	-28/-10	119/69	-28/-10	114/74	-18/-10	105/67	0/0	2	7	16		23	191	197	
PA	16	119/81	-18/-4	119/86	0/+2?	110/81	+4/+4	113/82	+2/0	1		34	95	31		298	321
CO	32	123/78	0/+2?	129/80	-12/0	123/81	-16/-10	124/75	-10/0		12	32	134		46	240	310
SP	40	117/83	0/-2	126/93	-6/-4					2	4			17	21		
MN	18					97/63	-12/-6	105/64	0/+16			3	87			20	197
PU	40	108/70	-14/-8							2				15			
AR	31	106/66	-10/0							1				22			
GO	24	115/68	-7/0							2				14			
MC	70			141/69	-18/-0										27		
ER	20			116/75	0/0												
WE	29																
HO	42					119/61	0/0	108/64	0/0								

P = blood pressure in mm. of Hg, systolic/diastolic.
ΔP$_{max}$ = maximum changes of pressures systolic/diastolic.

TABLE IV

Data on Hypertensive Patients

| Patient | Age (yr.) | Effect of Drug on Systolic and Diastolic Blood Pressure | | | | | | | | Duration of Drug Effect | | | | | | | |
| | | G3N | | NaNO₂ | | E+N | | M6N | | Beginning | | | | End | | | |
		P	ΔP max	P	ΔP max	P	ΔP max	P	ΔP max	G3N	NaNO₂	E+N	M6N	G3N	NaNO₂	E+N	M6N
MA	42	144/98	0/0	167/98	-14/0	156/98	0/0	146/99	0/0	2	8	44	38	34	35	674	267
FA	55	205/106	-24/0	220/119	-40/-8	220/116	-68/-28	213/110	-30/0	5	3	22	25	25	40	164	60
HU	61	179/90	+12/+12	168/95	-20/-10	186/94	-14/0	177/89	0/+12	1	3	13		20	44	361	
WH	61	163/87	-14/0	168/91	0/0	175/82	-20/-14	167/88	0/0	7		13	18	31		141	418
CN	64	206/110	-18/+6	209/119	0/0	188/94	0/-14	199/102	-10/-8	3			88	24			370
FD	20	184/103	-10/0	171/95	-22/0	160/101	0/0	160/94	0/+14	5					27		
FD				156/102							31				38		
DA	49	155/97	-20/0	174/106	-30/-8	171/109	-20/-14	151/109	0/-8	1	4	42	24	27	93	276	61
CK	42	169/113	-18/+4	182/117	-20/-6	160/105	+4/+14	163/101	-10/+8	1	6	99	42	19	82	478	478
AD	56	201/110	-60/-6	194/107	-24/-10	152/90	-20/-10	167/91	0/0	2	8	9		31	68	134	
RA	68	183/100	+10/+10	181/88	-8/0	170/88	+28/+8	182/89	-28/-18	12	5	9	34	23	39	154	214
TA	56			197/134	-42/-22						9				243		
TA	73	161/103	-12/-8	163/111	-12/-8	169/125	-34/-26	163/113	-20/-12	2	8	46	104	37	32	750	830
DU		208/101	0/0	200/94	+5/0	183/89	-20/-4			2	3	41		15	9	221	
DU		205/102	-20/0	199/94	-27/0					1	6			44	69		
LE	65	109/78	-68/-10	179/73	-18/+2			197/100	-20/-10	2	5		20	17	35		
SE	48	252/147	-29/-14					251/139	-52/-22	1			30	19			73
FR	74	225/107	-40/0					203/105	0/0	1				21			307
FR		210/110	-52/-10														
CA	47			210/165	0/0												
PO	58							207/106	0/0				37				
WN	31							227/171	-14/-14								119

drugs. With each drug a greater percentage of hypertensive patients exhibited a fall in blood pressure (except for erythrol tetranitrate) than of normal persons.

Untoward Reactions.—Of 32 subjects who received single doses of nitroglycerin, 8 had pounding headache, 1 had a hot feeling in the head, and 1 had dizziness. Of 28 subjects who received sodium nitrite, 1 had occipital pounding and 1 had nausea followed by vomiting. Of 24 who received erythrol tetranitrate, 4 had pounding headache. Of 28 who received mannitol hexanitrate, none had side effects. The untoward reactions were about evenly divided between normal and hypertensive subjects.

Of 15 patients who were given daily doses of mannitol hexanitrate in the clinic, 6 experienced such severe side effects that they were unable to continue taking the drug. Two others had effects that were mild and quickly disappeared during continuation of the regimes. The undesirable drug effects were: full feeling in the head, dizziness or headache, gastric discomfort without nausea or vomiting, abdominal cramp with nausea, mild diarrhea, and palpitation. Headache occurred in 4 cases, gastrointestinal symptoms in 4, palpitation in 2, and dizziness in one.
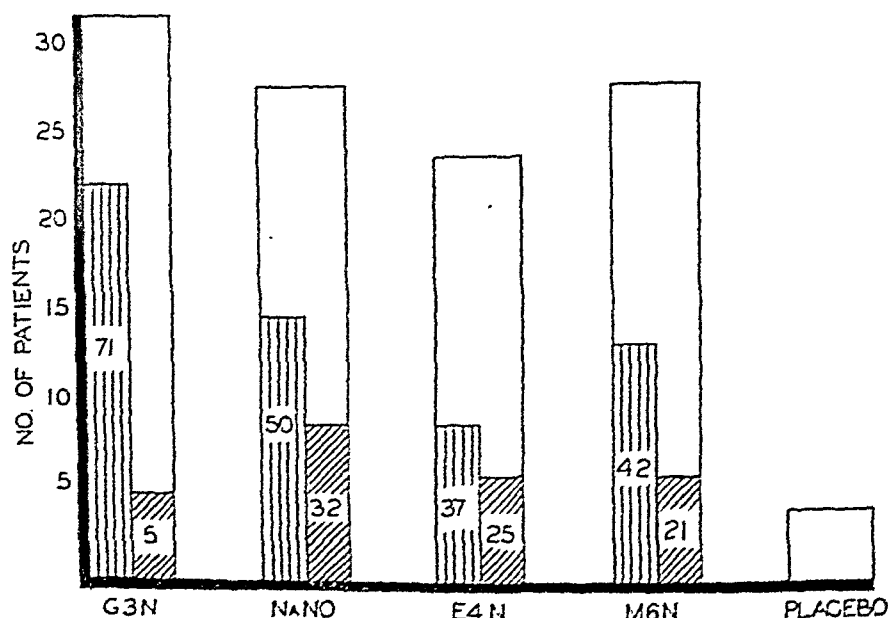
Fig. 3.—Number of subjects with each drug and percentage who showed a fall in blood pressure. The height of the open columns is the number of patients; the heights of the hatched areas give the number of patients in which a fall in systolic pressure (vertical hatch) and diastolic pressure (slant hatch) was observed, respectively. The numbers in the hatched areas represent the percentages of the patients who responded with lowered systolic and diastolic pressures, respectively.

DISCUSSION

Reliability.—For a given patient, the results with any one of these drugs are unpredictable. Some patients have no response, some have a lowering for only a short period of time, some have such a small fall in pressure that the drug seemingly will be worthless as an agent for

diminishing hypertension. There are a few ideal subjects. These have a good response that is sustained at a markedly lower level for a fairly long period. If a patient responds to one of these drugs, it does not mean that he will respond to any or all of the others. The only way in which the value of one of these drugs for a given patient can be judged is for that patient to take the drug, with several measurements of blood pressure after the administration of the drug at appropriate intervals.

The results with nitroglycerin were most reliable. We feel that this is because of its more rapid action, which is probably due to quicker and more constant absorption. Sodium nitrite was intermediate. Erythrol tetranitrate and mannitol hexanitrate were about equal; mannitol hexanitrate seemed to start its action a little later than erythrol tetranitrate, but the duration of maintained lowering was about the same for both. However, after mannitol hexanitrate, a larger percentage of subjects had a fall in blood pressure and there were fewer disagreeable side effects.

Symptomatic Relief.—In a group of 8 hypertensives who were followed for several months during treatment in the clinic with mannitol hexanitrate a fall in blood pressure could not be demonstrated. The important observation in this group was the relief of symptoms. This was often striking. In a control group of 11 patients, such definite symptomatic relief was not seen. Although the series is small, we feel that there is sufficient evidence to indicate the trial of this drug for long-standing hypertensives. If it relieves their symptoms, it is a worth-while therapeutic adjunct.[8, 9]

SUMMARY

1. Nitroglycerin, sodium nitrite, erythrol tetranitrate, mannitol hexanitrate, and a placebo were given to normal and hypertensive subjects, and blood pressure measurements were made at brief intervals until the effect of the drug was over. Each of the thirty-eight subjects received one or more of these substances, and most received all four "nitrite" drugs.

2. Of the subjects who were given these drugs, 51 per cent had a fall of systolic pressure, and 23 per cent had a lowering of diastolic pressure. The systolic fall was almost always greater than the diastolic. None had a fall in blood pressure after the administration of a placebo.

3. The amount of the fall in blood pressure in hypertensive patients varied greatly, but the averages were as follows: nitroglycerin, 16/4 mm. Hg, sodium nitrite, 21/1 mm., erythrol tetranitrate, 14/5 mm., and mannitol hexanitrate, 12/4 mm. In normal subjects, the average fall in blood pressure was as much as 10 mm. less than the corresponding figure for hypertensives.

4. The period between the administration of the drug and the beginning of the fall in blood pressure was variable. For nitroglycerin this

interval averaged 2 minutes; for sodium nitrite, 7 minutes; for erythrol tetranitrate, 35 minutes; and for mannitol hexanitrate, 55 minutes after the drug was given.

5. The average duration of blood pressure lowering was as follows: nitroglycerin, 20 minutes; sodium nitrite, 62 minutes; erythrol tetranitrate and mannitol hexanitrate, about the same, 256 and 252 minutes, respectively. With the last two drugs there was wide variation in the duration.

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CONGESTIVE HEART FAILURE AND ELECTROCARDIOGRAPHIC ABNORMALITIES RESULTING FROM EXCESSIVE DESOXYCORTICOSTERONE ACETATE THERAPY IN THE TREATMENT OF ADDISON'S DISEASE

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THE phenomenon of fluid and salt retention resulting from the treatment of Addison's disease with desoxycorticosterone acetate has been described by many observers.[1-8] In fact, it has been noted that the patient may succumb in the course of a few days as a result of the excessive accumulation of fluid when an excess of desoxycorticosterone acetate is given. The complimentary effect of sodium and desoxycorticosterone acetate has been stressed, and the hazards of giving large doses of desoxycorticosterone acetate or desoxycorticosterone acetate and sodium chloride are therefore self evident.

In recent months, we have had two patients who developed congestive heart failure as the result of taking excessive amounts of desoxycorticosterone acetate and salt. The changes in the electrocardiograms were quite striking, and, as will be pointed out later, a good deal of information was gained from a comparison of the serial changes. Although, as stated above, numerous observers have described the hazards of giving too much desoxycorticosterone acetate in Addison's disease, the striking effect upon the electrocardiogram has not been adequately emphasized.

REPORT OF CASES

CASE 1.—A 45-year-old housewife entered the hospital Aug. 28, 1939, complaining of weakness of two years' duration. In December, 1937, her blood pressure had been found to vary from 150/104 to 160/110. She had lost 18 pounds in weight during the year before entry. Physical examination revealed a rather nervous woman with moderate, dusky-brown pigmentation of the skin of the forearms, hands, and neck. The heart was normal and the blood pressure was 90/65. On Aug. 31, 1939, the blood sodium was 141 meq./L. However, on a salt-deprivation, high-potassium test (Cutler-Power-Wilder test), the blood sodium fell to 128 meq./L. and blood chlorides to 85 meq./L. on the second day of the test. She was discharged on a high salt intake.

In May, 1940, because of irregular menses, she received a sterilization dose of x-ray to the pelvis. She returned to the hospital October 30, complaining of considerable weakness and abdominal pain lasting twenty-four hours. Her blood pressure (recumbent) was 82/60. She was given desoxycorticosterone acetate, 10 mg. intramuscularly, daily for seven days, after which she received four pellet implantations total-

ing 508 milligrams. No extra salt was given. On Nov. 15, 1940, the blood sodium was 142 meq./L., and the potassium, 3.5 meq./L. The patient returned to the hospital March 1, 1941, complaining of weakness for six weeks; at this time her blood pressure was 90/50, and her weight was 91 pounds. Two more pellets were implanted, totaling 250 milligrams.
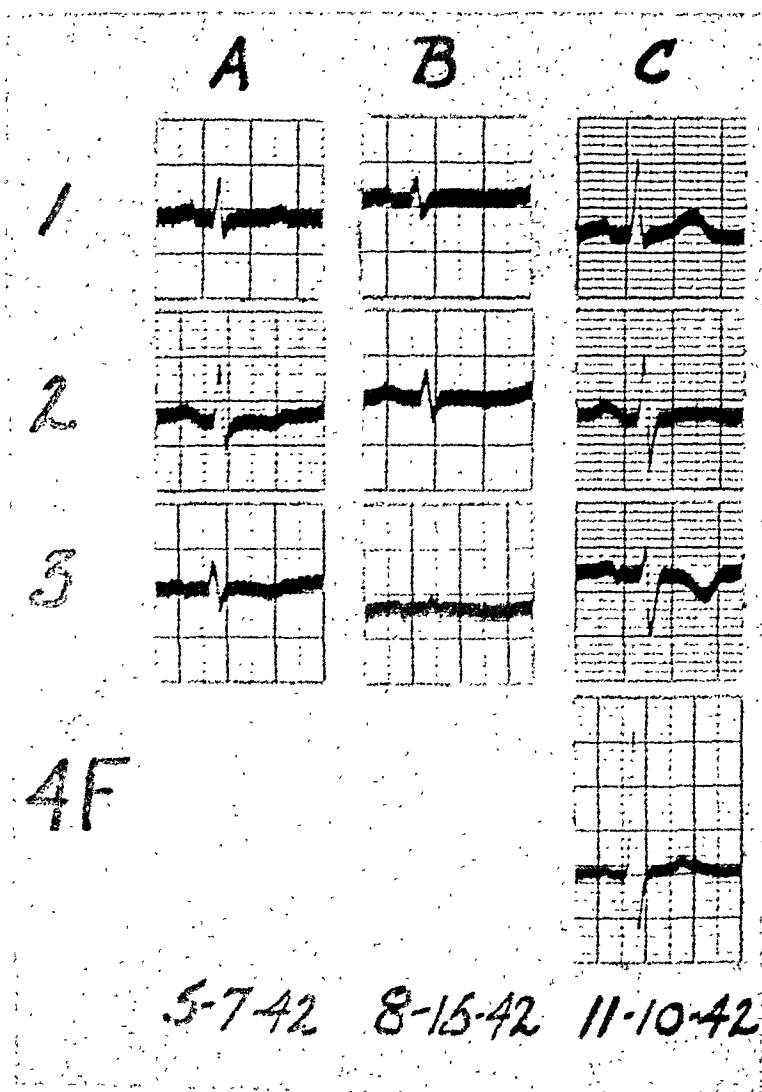
Fig. 1.—Serial Electrocardiograms in Case 1. The relatively low voltage of the QRS and T waves on May 7, 1942, suggests a slight excess of the drug. By Aug. 15, 1942, the full effect of desoxycorticosterone acetate overdosage is manifest in the electrocardiogram, with isodelectric or ⋯⋯ ⋯ ⋯ in Leads I and II. After diuresis and disappearance of ⋯ ⋯ ⋯ ⋯ ⋯ with adequate daily substitution of desoxycorticosterone ac ⋯ ⋯ ⋯ had returned essentially to normal on Nov. 10, 1942. The patient had not had digitalis for two weeks.

The patient's health was quite good, and her strength was adequate until she returned in May, 1942, with recurrence of the weakness for a period of one month. The blood pressure was 110/75, and the blood sodium was 140 meq./L., however. The electrocardiogram at that time is shown in Fig. 1, A. Five pellets were then implanted, totaling 634 milligrams. On May 17, she noted some edema of the face and legs, and, on May 25, her blood pressure was 160/86, and her blood sodium,
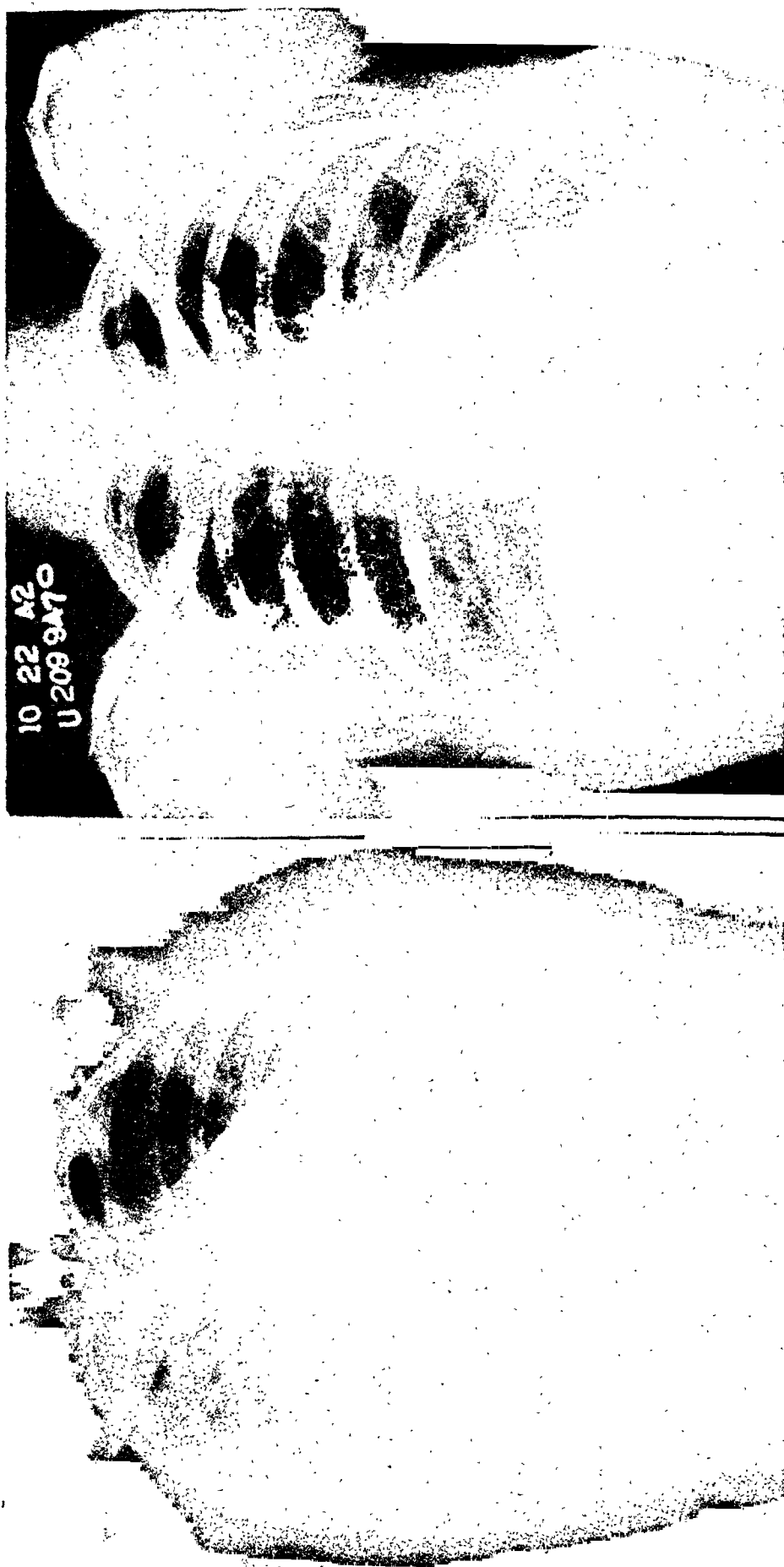
Fig. 2.—*A*, Bedside roentgenogram of the chest in Case 1, made on Aug. 24, 1942, showing cardiac enlargement and congestion of the lungs, particularly on the right. *B*, Teleoroentgenogram of the chest of the same patient on Oct. 22, 1942, revealing clear lung fields and a heart of normal size.

150 meq./L. The 3 Gm. of extra salt in her diet were discontinued. By July 22, the weight increased to 119 pounds, and her blood pressure was 126/92. The urine showed 2 plus albumin. She was readmitted to the hospital at this time because of abdominal swelling of two weeks' duration. There was some swelling of the face, shifting dullness was demonstrated in the abdomen, and the blood pressure was 128/104. No edema of the ankles was noted. Blood chemical studies revealed the following: nonprotein nitrogen, 13 mg. per cent; chloride, 111 meq., sodium, 146 meq., and potassium, 4 meq./L. A roentgenogram of the chest revealed an enlarged heart (transverse diameter, 12.9 cm., as compared to 10 cm. several months before).

On August 1, two of the five previously implanted pellets were removed. The electrocardiogram on August 15 is shown in Fig. 1, B. Three injections of 0.5 c.c. of mercupurin were without striking effect. On August 21, the three remaining pellets of desoxycorticosterone acetate were removed, and she was given 15 c.c. of cortical extract daily. The following day the venous pressure was 28 cm. of water, and the arm-to-skin circulation time was 21 seconds. A bedside roentgenogram of the chest was made on August 24, and is illustrated in Fig. 2, A. A diastolic gallop rhythm was noted at the apex of the heart. Edema over the sacrum was prominent, and the patient was orthopneic. On August 29, 1 c.c. of mercupurin was given, and the urinary output was 1,500 c.c. during the subsequent twenty-four hours. The blood pressure averaged about 130/90, and the weight remained at 118 pounds. Digitalis was then started, on September 4, in a dose of 0.13 Gm. each day, and within eight days the patient lost twenty pounds in weight, the gallop rhythm disappeared, and the heart decreased in size. The digitalis was then decreased to 0.065 Gm. every day, and the patient's condition improved rapidly. On September 25, the venous pressure was 11 cm. of water and the arm-to-skin circulation time was 19 seconds. On October 5, the electrocardiogram had shown striking improvement. The patient was discharged on October 26, at which time the digitalis was discontinued and she was receiving 1 mg. of desoxycorticosterone acetate daily, without extra salt. The weight fluctuated from 96 to 102 pounds, and the blood pressure varied from 160/120 to 120/80. The patient felt better than she had for many months. No signs of congestive heart failure or edema remained, and no digitalis was necessary. Another roentgenogram of the chest (Fig. 2, B) revealed remarkable improvement. On November 10, the electrocardiogram was normal. She has continued to do well, receiving daily injections of 1 mg. of desoxycorticosterone acetate. The electrocardiogram taken in July, 1943, was essentially the same as that of November, 1942.

Comment.—The clinical diagnosis of Addison's disease was clear-cut in this patient, who had been observed to have hypertension previously. In retrospect, there is little doubt that the weakness which developed in May, 1942, was not due to adrenal insufficiency. The blood sodium was normal, the blood pressure was normal, and the electrocardiogram suggested, if anything, an excessive absorption of desoxycorticosterone acetate. The subsequent course, with the appearance of definite signs of congestive heart failure after the implantation of more desoxycorticosterone acetate, was dramatic, and the low voltage of the QRS and T waves of the electrocardiogram was equally noteworthy. After the

removal of the subcutaneous pellets, the response to relatively small doses of digitalis was equally dramatic, and the electrocardiogram returned to normal. It should be noted, however, that the desoxycorticosterone acetate pellets had been removed, and that the patient might have had a spontaneous diuresis without the aid of digitalis.

CASE 2.—An 18-year-old girl entered the hospital Aug. 11, 1942, complaining of recurrent attacks of abdominal pain, with nausea, vomiting, and weakness, of twelve months' duration. In January, 1942, appendectomy was done because of one of the attacks of abdominal pain, and it was said that the patient collapsed during the operation. There had been no menses for four months before entry.
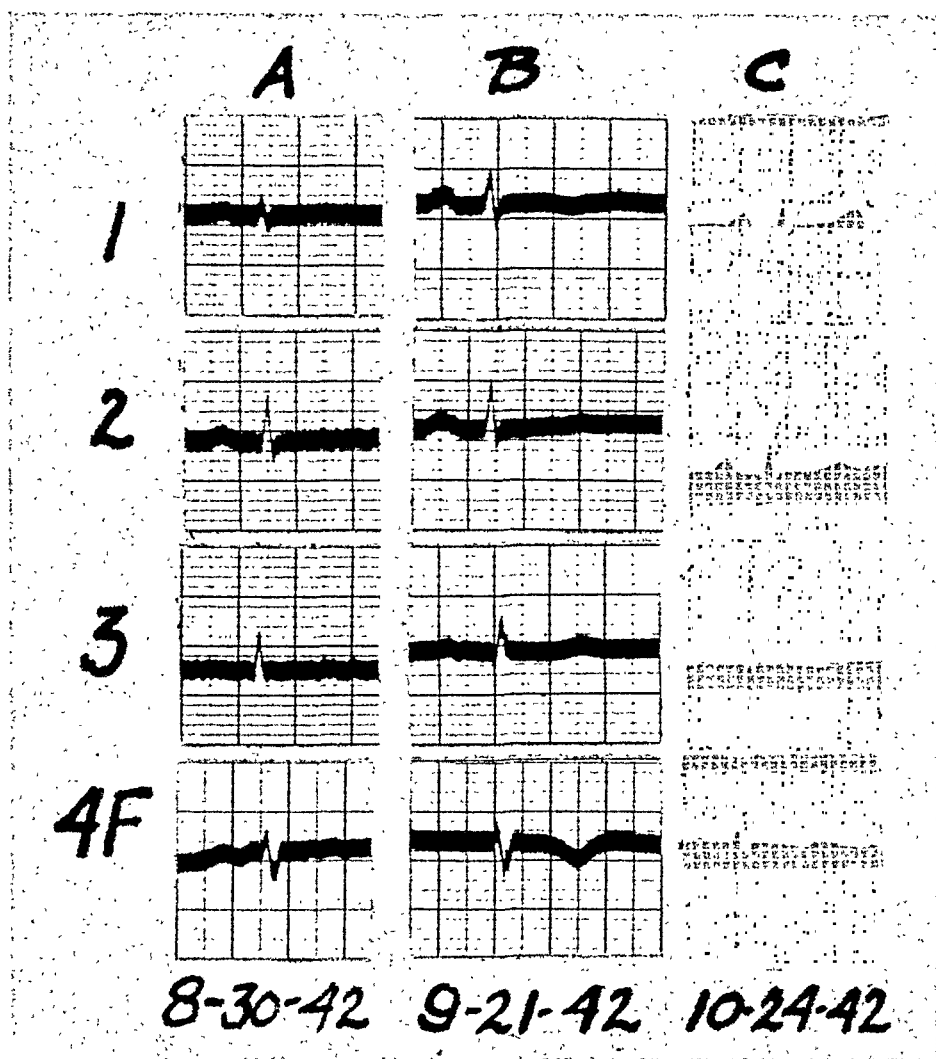
Fig. 3.—Serial Electrocardiograms in Case 2. The first electrocardiogram, Aug. 30, 1942, shows the effect of excessive doses of desoxycorticosterone acetate which was still present on Sept. 21, 1942. The T waves in Leads I and IV were inverted, and the Q-T interval had increased to 0.40 second, although the heart rate at this time was 60. The low voltage of the QRS, and very low, isoelectric, or slightly inverted T waves should be noted. By Nov. 24, 1942, the electrocardiogram had improved remarkably, as had the patient. On May 17, 1943, the T wave in Lead IV had become positive (0.5 mm.), and the limb leads were essentially the same.

Physical examination revealed a restless, nervous girl with evidence of recent weight loss. There was characteristic pigmentation of the lips, hard palate, and abdominal scar. The heart was normal and the blood pressure was 70/40 (recumbent). Blood chemical examination revealed: sodium, 128 meq./L. sugar, 61 mg. per cent, and nonprotein nitrogen, 90

mg. per cent. On August 14, the patient received 10 c.c. of cortical extract and 20 mg. of desoxycorticosterone acetate. During the subsequent four days she received 125 c.c. of cortical extract, 105 mg. of desoxycorticosterone acetate, and 59 Gm. of salt. On August 19, some edema of the eyelids was noted, the blood pressure was 90/60, the chest roentgenogram revealed increased density of the lower lung fields which was consistent with pulmonary edema, and chemical examination of the blood revealed a chloride of 112 meq./L., a nonprotein nitrogen of 15 mg. per cent, and sugar of 145 mg. per cent. Desoxycorticosterone was then discontinued, and the patient received cortical extract in a dose of 15 c.c. daily. The signs in the chest decreased until August 28, when the patient received 7.5 mg. of desoxycorticosterone, after which she gained 5 pounds, the signs of pulmonary congestion returned, and the electrocardiogram (on August 30) was as shown in Fig. 3, A.

Desoxycorticosterone acetate was again discontinued, except for a mistaken dose of 20 mg. on September 2, and the patient was maintained on 15 c.c. of cortical extract without extra salt. Her condition changed little. There was some dependent edema, and, on September 9, the heart was found to be enlarged roentgenologically (an increase in the transverse diameter of 4.5 cm., i.e., from 8.9 to 13.4 cm., with poor pulsation fluoroscopically). The two roentgenograms are shown in Fig. 4. The same day the venous pressure was 15 cm. water, the intensity of the pulmonary second sound was moderately increased, and there was gallop rhythm at the apex. Digitalis, in a dose of 130 mg. daily (U.S.P. XI), was given for nine days, after which she received 65 mg. daily for five weeks. The twenty-four-hour excretion of the 17 ketosteroids on September 17 was 1.1 mg. per cent.

An electrocardiogram, taken on September 21, at which time the heart had changed little roentgenologically, although the gallop had disappeared, is shown in Fig. 3, B. By October 1, the transverse diameter of the heart shadow had decreased considerably (to 11 cm.), the body weight had decreased from one hundred eleven to one hundred pounds, and there was no detectable edema. The patient had her first menstrual period in six months on October 6. The dose of desoxycorticosterone acetate and cortical extract was progressively decreased, and she was discharged on October 25, taking 5 c.c. of the extract and 2 mg. of desoxycorticosterone a day.

Comment.—There was a good deal of delay in initiating the treatment of adrenal insufficiency, so that, when the diagnosis was made, unusually large amounts of desoxycorticosterone acetate were given, together with an abundance of sodium chloride. The signs of congestive heart failure were as definite as in Case 1, and the serial electrocardiograms were as remarkable. The shallow inversion of the T wave in Leads I and IV on Sept. 21, 1942, was no doubt indicative of moderate damage to the myocardium incident to the effect of excessive amounts of desoxycorticosterone acetate. The patient was receiving digitalis at the time, but in relatively small doses. Pericarditis was considered as a cause for the inversion of the T waves, but no positive evidence was ever obtained to substantiate such a diagnosis. It should be noted, likewise, that the signs of congestion developed while the blood pressure was still below normal, and without any significant tachycardia.
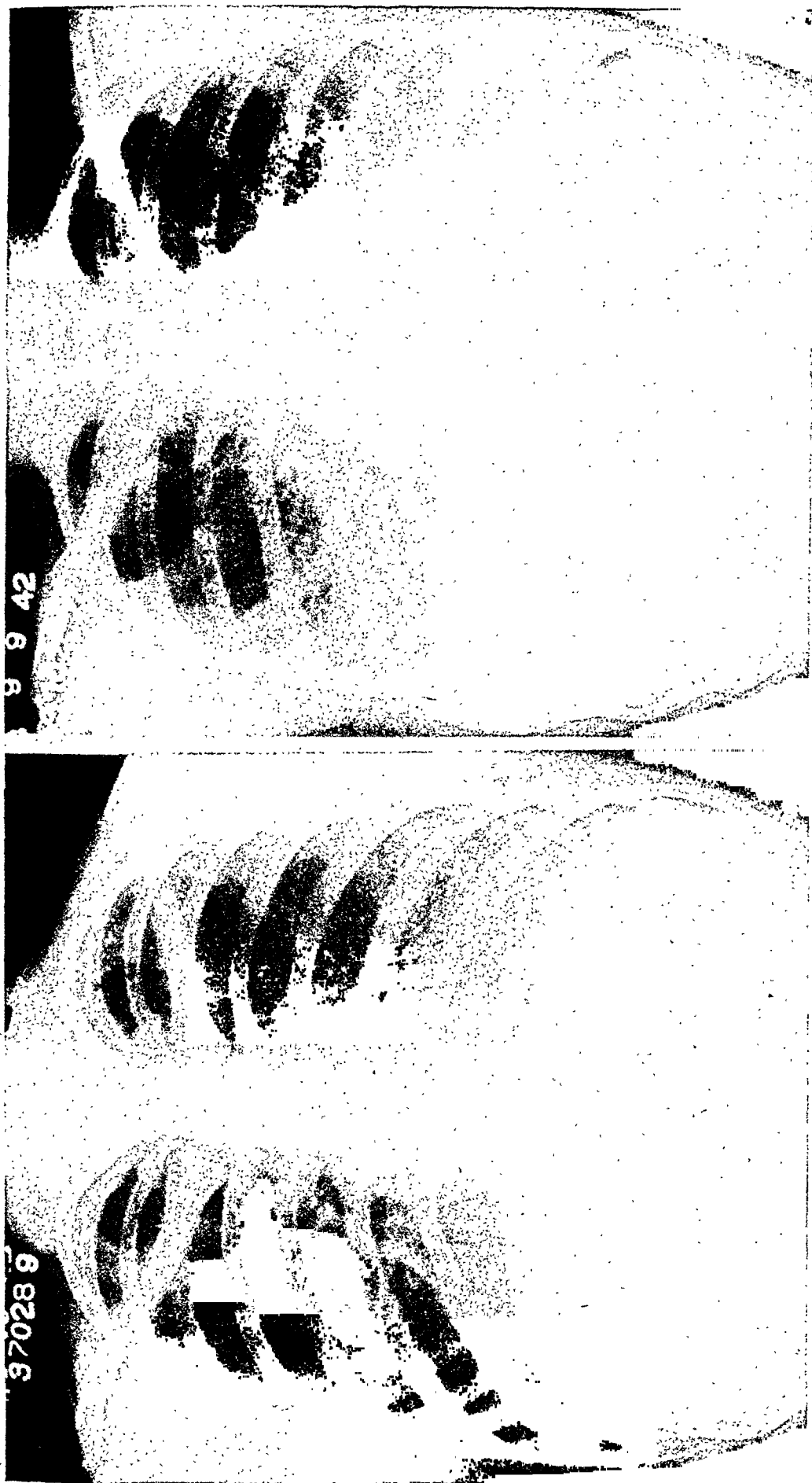
Fig. 4.—*A*, Teleorentgenogram of the chest in Case 2, made Aug. 13, 1942, before any specific therapy. The heart is small and the lung fields are clear. *B*, Repeat teleoroentgenogram of the chest on Sept. 9, 1942, showing enlargement of the heart and moderate pulmonary congestion at the bases.

DISCUSSION

The mechanism of the heart failure in these two cases is not entirely clear. That there was an accumulation of salt and water in the body there can be little doubt, as evidenced by the increase in body weight and the development of edema. The evidence of congestive heart failure was likewise clear, namely, the increase in the size of the heart, the roentgenologic signs of pulmonary congestion, the gallop rhythm, and the rise in venous pressure. The striking rise of blood volume that occurs after the administration of desoxycorticosterone acetate to patients with Addison's disease[1] was undoubtedly an important factor in causing the congestive heart failure. This also was a factor in increasing the first patient's blood pressure to hypertensive levels.

However, a disturbance of electrolytic balance was undoubtedly of some importance in the altered physiology of the heart and the decreased efficiency of the heart muscle. It was demonstrated many years ago by Ringer[9] that potassium in proper concentration is essential for normal contraction of cardiac musculature. More recently, Follis, et al.,[10, 11] have observed morphologic changes in the cardiac muscle of rats which were maintained on a low potassium diet and forced to exercise. Similar changes were not noted in the voluntary muscles, and the changes in the cardiac muscle were not observed in control animals which received an adequate amount of potassium in the diet. Darrow and Miller[12] produced similar morphologic changes in rats and cats by daily injection of desoxycorticosterone acetate, and these, too, were prevented in control animals by the addition of potassium to the diet. It seems not unreasonable, therefore, to suppose that similar changes may have taken place in these two cases during the period when the patients were receiving excessive amounts of desoxycorticosterone acetate, which, of course, would be an important factor in the development of congestive heart failure. The serum potassium was measured in only one of these patients, and was found to be within the range of normal. This determination, however, does not indicate the status of the potassium metabolism in either the cardiac or skeletal musculature, for such stores may be depleted without appreciably affecting the serum potassium. A more accurate means of following the loss of potassium would be to ascertain the urinary excretion, which, unfortunately, was not followed in these patients. The improvement of the patients after relatively small doses of digitalis suggests that digitalis may be used to advantage in controlling or preventing the heart failure. At least, in the event of the development of congestive heart failure, digitalis should be given.

The serial changes in the electrocardiograms were quite striking, and this phenomenon, too, is undoubtedly associated with the altered electrolytic balance which occurs after prolonged treatment with desoxycorticosterone acetate, with particular regard to potassium. With the loss of cellular potassium in familial periodic paralysis,[13, 14] rather

striking alterations in the electrocardiogram have been observed, particularly loss of amplitude of the T waves. Similar but less marked changes have been observed to occur in the electrocardiogram when normal men are given desoxycorticosterone acetate for short periods of time in good-sized doses.[15]

During the treatment of patients with Addison's disease by desoxycorticosterone, the question frequently arises as to whether the patient has had too little or too much of the synthetic hormone. This is true because weakness may be the predominant symptom in either case. The weakness caused by excessive amounts of desoxycorticosterone acetate may well be associated with the loss of body potassium which results therefrom, and is to be likened to the weakness and paralysis of familial periodic paralysis. For this reason it seems wise to give small to moderate doses of potassium salts to patients suffering from excess desoxycorticosterone acetate therapy. There is usually a gain in weight after desoxycorticosterone acetate therapy, but this at times is not very striking, for some return of the weight toward normal is expected. The size of the heart is known to be an accurate index in treating Addison's disease, but comparable roentgenograms are often difficult to obtain. Serial electrocardiograms seem to be a reliable index of the status of desoxycorticosterone acetate therapy, and can be used to advantage, particularly in ascertaining whether a patient has had an excess of the synthetic hormone.

SUMMARY AND CONCLUSIONS

Congestive heart failure and electrocardiographic changes were observed in two cases of Addison's disease in which an excessive amount of desoxycorticosterone acetate was given. The cause of the decreased efficiency of the heart is discussed, and the striking alterations in the electrocardiogram (low voltage of QRS waves and flattening or inversion of the T waves) are emphasized. The changes in the electrocardiogram, particularly the T-wave changes, have been compared with the alteration of the electrocardiogram incident to a loss of body potassium. Digitalis therapy proved of considerable value in clearing up the congestion in the two cases reported here. Potassium salt by mouth may be of value in improving the efficiency of the heart muscle during desoxycorticosterone acetate toxicity.

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ADDENDUM

Since submitting this manuscript for publication three relevant reports have appeared[16-18] in the literature. The last two reports[17, 18] further emphasize the role that potassium metabolism plays in myocardial physiology during toxicity from desoxycorticosterone acetate.

AN INTERPRETATION OF AXIS DEVIATION AND VENTRICULAR HYPERTROPHY

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BRONX, N. Y.

INTRODUCTION

IN 1913, Einthoven, Fahr, and deWaart[1] developed the concept of the electrical axis and a method of measuring it in terms of the angle α.†

This concept has been of great value because it has been found that there is good clinical correlation between the recognized electrocardiographic patterns of axis deviation and conditions in which hypertrophy of the right or left ventricle exists.

Yet, as is well known, the electrical axis is not fixed, but changes from moment to moment during the inscription of the QRS complex,[2] and what is ordinarily described as the electrical axis is the reading taken at the peak of the R wave. Furthermore, in cases of right or left ventricular hypertrophy, reference to the electrical axis does not explain the RS-T deviations and T-wave changes which are often observed. In addition, there are many atypical cases of ventricular hypertrophy which do not conform to the established criteria, such as cases of left ventricular hypertrophy in which there is right axis deviation.[3] Finally, although there is a close correlation between angle α and the average direction of spread of the impulse in the auricles, no such clear correlation is found in the ventricles.

If, instead of standard leads, unipolar extremity leads (Wilson's ordinary unipolar extremity leads,[4] or the author's augmented unipolar extremity leads [aV-leads][5]) are used, interpretation of axis deviation is simpler, because each unipolar extremity lead varies directly with the electrical axis of the heart.[6] But even with these leads, the explanation of physical changes, such as hypertrophy of the ventricles, in terms of the angle α is hard to grasp, especially when the angle α has negative values.

It was therefore felt that a graphic analysis by which the electrical activity of the ventricles could be interpreted in terms of the actual spread of the impulse through the muscle, rather than a mathematical calculation of the angle α at particular instants, might prove of value. We found the answer to this problem in the method we were using to analyze the patterns of unipolar leads.

In brief, the principles underlying this method of interpretation of axis deviation and ventricular hypertrophy are the following: All unipolar electrocardiograms (whether extremity, precordial, or thoracic), irrespective of the location of the electrode, record the electrical activity of the heart as a whole, rather than favoring selective, small areas which may lie beneath the electrode.

An analogy may make this clearer: If a roentgenogram of the chest be taken, all the structures of the thorax are visualized, irrespective of whether the patient stands facing the x-ray tube (a-p position), or with his back to the tube (p-a position). The characteristics of the roentgenogram, however, will depend on many factors; for example, in the one taken in the first position, the heart will appear larger than in the second, because, in the first position, the heart was nearer to the x-ray tube.

Similarly, the characteristics of such electrocardiograms will also depend on several factors, namely: (a) The direction in which the electrical activity is spreading over the muscle, (b) the direction in which the regression of activity takes place, (c) the location of the electrode, (d) the distance of the electrode from the region of electrical activity, and (e) the size and shape of the ventricles.[*][7]

The easiest way to grasp this concept is to begin with an explanation of the electrical activity of a simple muscle strip immersed in an extensive and uniform conducting medium, as recorded in the electrogram.[†]

To consider in more detail the five factors mentioned above: (a) and (b) *The Activation and Regression of Electrical Activity.*—It may be stated as a general rule that the wave of activation, which is quite rapid in muscle, has a (+) pole in the direction to which the impulse is spreading, and a (−) pole in the direction from which the impulse is passing[7,8] (Fig. 1).

During the regression of electrical activity, which is a comparatively slow process, these conditions are reversed, and the (−) pole is in the direction to which the regression wave is passing (Fig. 1). Since muscle which has become activated does not stay in this state very long, the regression of activity starts soon after activation has begun, and, therefore, these two phases are going on simultaneously in different segments of the muscle mass for the greater period of the electrical activity in the muscle.

(c) *The influence of the Position of the Electrode.*— The influence of the position of the electrode on the individual deflections of the electrogram can also be seen in Fig. 1. In this example, the waves of activation and of regression travel in the same direction. An electrode at *F* will face the tail end of the wave of activation, and, consequently, will record

(–) potentials throughout the period when the muscle is being activated. During the regression of activity, the electrode, also facing the tail end of the wave, now records a (+) deflection. An electrode at H will record an electrogram just the opposite to that at F, because, here, the electrode is always facing the oncoming waves of activation and regression.

With an electrode at G the following conditions hold: Up to the moment the wave of activation reaches the muscle immediately under G,
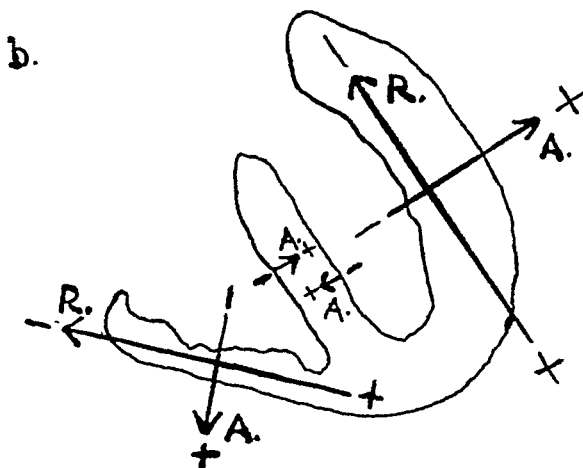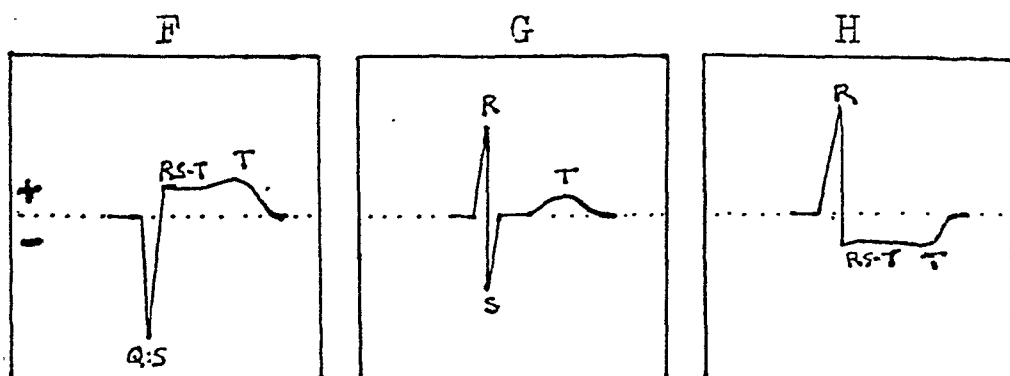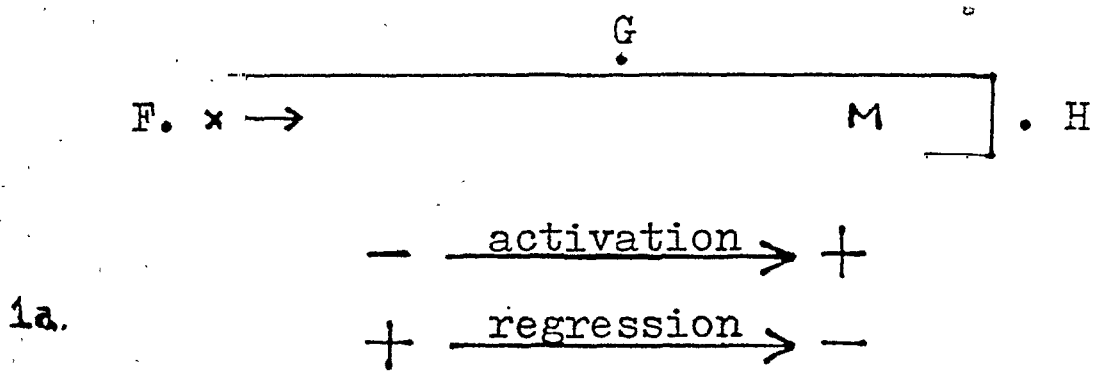
Fig. 1.—a, Electrical activity in a simple muscle strip immersed in an extensive and uniform conducting medium and recorded in the electrogram (after Macleod[7]). M = muscle strip, x = place of origin of the impulse, and F, G, H = electrograms which might be recorded if the electrodes were placed as in the sketch. It is assumed that, for each of the records, the other electrode (not shown) is so distant from the muscle that its potentials are negligible. The arrows indicate the direction in which the waves of activation and regression pass, and the polarities of the wave fronts.

b, Schematic representation of the paths of activation and of regression in the ventricles of the normal heart. A = activation, R = regression. The heart is shown in horizontal cross section as in Fig. 2c.

the electrode is facing the (+) pole of the wave, and a (+) deflection is recorded. During the remaining period of activation the electrode, facing the tail end of the wave, records a (−) deflection.

With respect to the regression of activity, up to the moment the regression wave reaches the muscle under G, the electrode has been facing its (−) front pole. This deflection is hidden within the QRS complex,[7] and the only portion of the regression wave clearly observed is that recorded during the latter stages of regression, when the electrode is facing its tail (+) end.

From the foregoing, the following conclusions may be drawn:

a. Although activation and regression of electrical activity go on simultaneously throughout the greater part of the electrical activity in the muscle, the QRS, in a general way, may be considered to be caused by the activation of the muscle, and the RS-T segment and the T wave to be caused by the regression of electrical activity.

b. The RS-T segment may lie above, on, or below the isoelectric line, and T may be (+) or (−), depending on the location of the electrode, other factors remaining equal.

c. When the waves of activation and regression travel along similar paths, the RS-T segment and T wave will tend to point in a direction opposite to the QRS.

d. *The Effect of the Distance Between the Electrode and the Region of Electrical Activity.*—The effect of the electrical activity on the electrode is inversely proportional to the square of the distance of the electrode from the source of the electrical activity.[7] Thus, if the electrode were moved from a point 3 cm., to one 6 cm., away from the region being activated, there would be a fourfold decrease in potential recorded, although the electrode was moved only twice as far from the active region.

The previously mentioned relations have been expressed mathematically,[7,8] but need not be considered for the purposes of this paper.

e. *The Size and Shape of the Ventricles.*—These facts can be applied directly to the study of the human heart, if the following additional factors are taken into consideration and unipolar leads are used:[e]

1. The ventricles are not a simple muscle mass, but may be likened to two curved muscles joined at their adjacent ends by the interventricular septum to form an asymmetrical, cup-shaped muscle with its open end facing the head and right shoulder girdle[11] (Fig. 2).

The relations of the ventricles to the chest wall can be observed also in Fig. 2. It should be noted that practically all of the ventricular muscle lies to the left of the sternum; that the right ventricle lies in relation to the anterior chest wall; that the left auricle faces posteriorly (Fig. 2, *b*); and that the left ventricle actually overlies the diaphragm, and faces, for the most part, inferiorly.

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*It is also assumed that the current produced within the heart is distributed uniformly throughout the body, and that the Einthoven triangle hypothesis is correct. Although this has been denied by some,[8] recent work serves to substantiate it.[9,10]
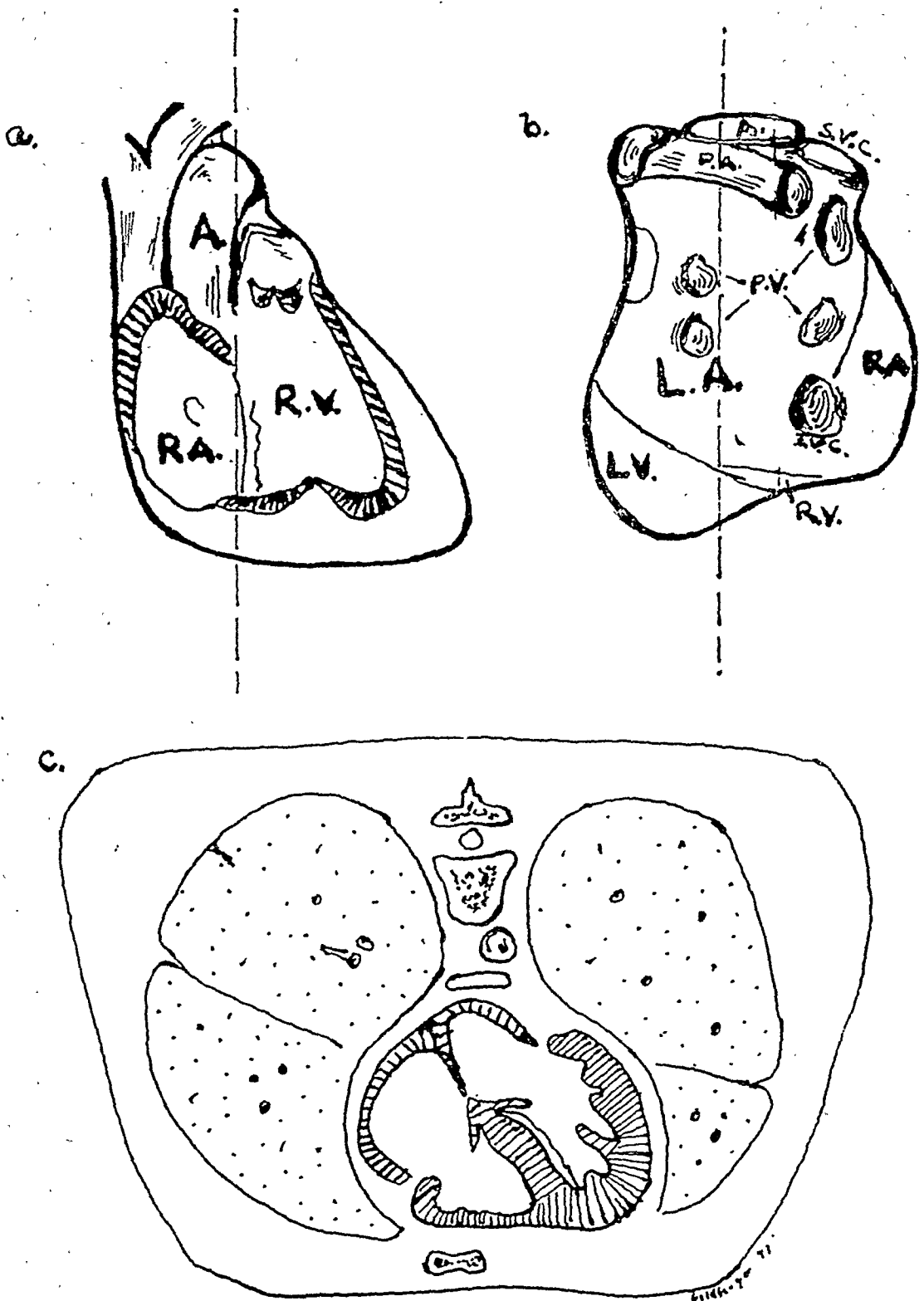
Fig. 2.—The relations of the heart to the thoracic cage. Vertical dotted lines represent the midline of the body. A = Aorta, RA = right atrium, RV = right ventricle, LV = left ventricle, PA = pulmonary artery at its bifurcation (at level of fifth dorsal vertebra), PV = pulmonary veins, SVC = superior vena cava, IVC = inferior vena cava, and LA = left atrium. a, Anterior view of the heart (after Cunningham[13]). The anterior walls of the right ventricle and right atrium and part of tricuspid valve have been removed.

b, Posterior view of the heart (after Cunningham[13]).

c, Cross section through chest at level of sternal end of fourth costal cartilage and eighth dorsal vertebra (after Eycleshymer and Shoemaker[21]).

2. Although the spread of the impulse is not even throughout the ventricles, the general direction of spread is from the subendocardial region of each ventricle outward to the epicardium of each ventricle.[*] Therefore, an electrode so placed that it faces the oncoming wave of activation in one of the ventricles is also facing, to some extent, the tail end of the activation wave in the other ventricle (Fig. 1, *b*).

3. A further complication arises from the fact that, normally, the thickness of the left ventricle is greater than that of the right. Consequently, the surface of muscle in the left ventricle in a state of partial activation or partial regression will tend to be greater than in the right ventricle; therefore, the electrical activity of the left ventricle will tend to dominate the electrocardiographic pattern.[†]

4. Unlike in the simple muscle strip, here the path of activation is different from the path of regression.[12] Therefore, T will tend to point in the same direction as QRS (Fig. 3).

MATERIAL AND METHOD

Although we have on file unipolar leads of more than 3,000 patients, in over 400 of whom multiple unipolar precordial leads were taken, for this particular study we selected 30 additional, adult subjects: 10 normal subjects; 10 patients with evidence of left ventricular preponderance in the electrocardiogram; and 10 with evidence of right ventricular preponderance.[‡]

In addition to the standard leads, the following unipolar leads (taken with the author's indifferent electrode of zero potential[5]) were used:

1. From the right arm (aVr lead).
2. From the left arm (aVl lead).
3. From the left leg (aVf lead).
4. R.S.Cl. lead, with the electrode at the apex of the supraclavicular region at the right midclavicular line.
5. Head lead, with the electrode at the angle of the left side of the mandible. In this connection, we conducted preliminary experiments and took records not only from various positions on the surface of the face and head, but also the tongue. All records were practically identical. Furthermore, when two electrodes were placed on the head and the potential difference measured, it was found that the string did not move at all, or minimal deflections were recorded. The head, therefore, for practical purposes, may, like the extremities, be considered as a volume conductor.
6. L.S.Cl. lead, similar to the R.S.Cl. lead.
7. R.U.Sc. lead from the base of the spine of the right scapula.
8. 2 R.M.Ax. lead, from the right axilla in the second intercostal space on the midaxillary line.
9. 2 R.M.Cl. lead, from the second intercostal space in the right midclavicular line.

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[*] It is assumed that the spread of activity from the subendocardial region of both sides of the septum inward serves to neutralize the effect of this activity on the electrocardiogram. However, recent work of ours[21] indicates that in many, if not in all, normal cases, the left side of the septum is activated before the right. This, if so, would serve to modify the initial QRS deflection only, and not the main ventricular deflection.

[†] There are no potential differences within a mass of fully active or inactive muscle. Therefore, such a region does not affect the electrocardiogram as long as this state continues.

[‡] Also see Appendix.

I	II	III	R.Arm	L.Arm	L.Leg

V-1	V-2	V-3	V-4	V-5	V-6

	R.S.Cl.	Pend	L.S.Cl.		

| 2 | 2 | 2 | 2 | | |
| R.U.Sc. | R.M.Ax. | R.M.Cl. | L.M.Cl. | L.M.Ax. | L.U.Sc. |

| 5 | 5 | | | | |
| R.L.Sc. | R.L.Ax. | R.L.Cl. | V-4 | V-6 | L.L.Sc. |

| 12 | 12 | | | 12 | 12 |
| R.L.B. | R.L.Ax. | R.U.A. | L.U.A. | L.L.Ax. | L.L.B. |
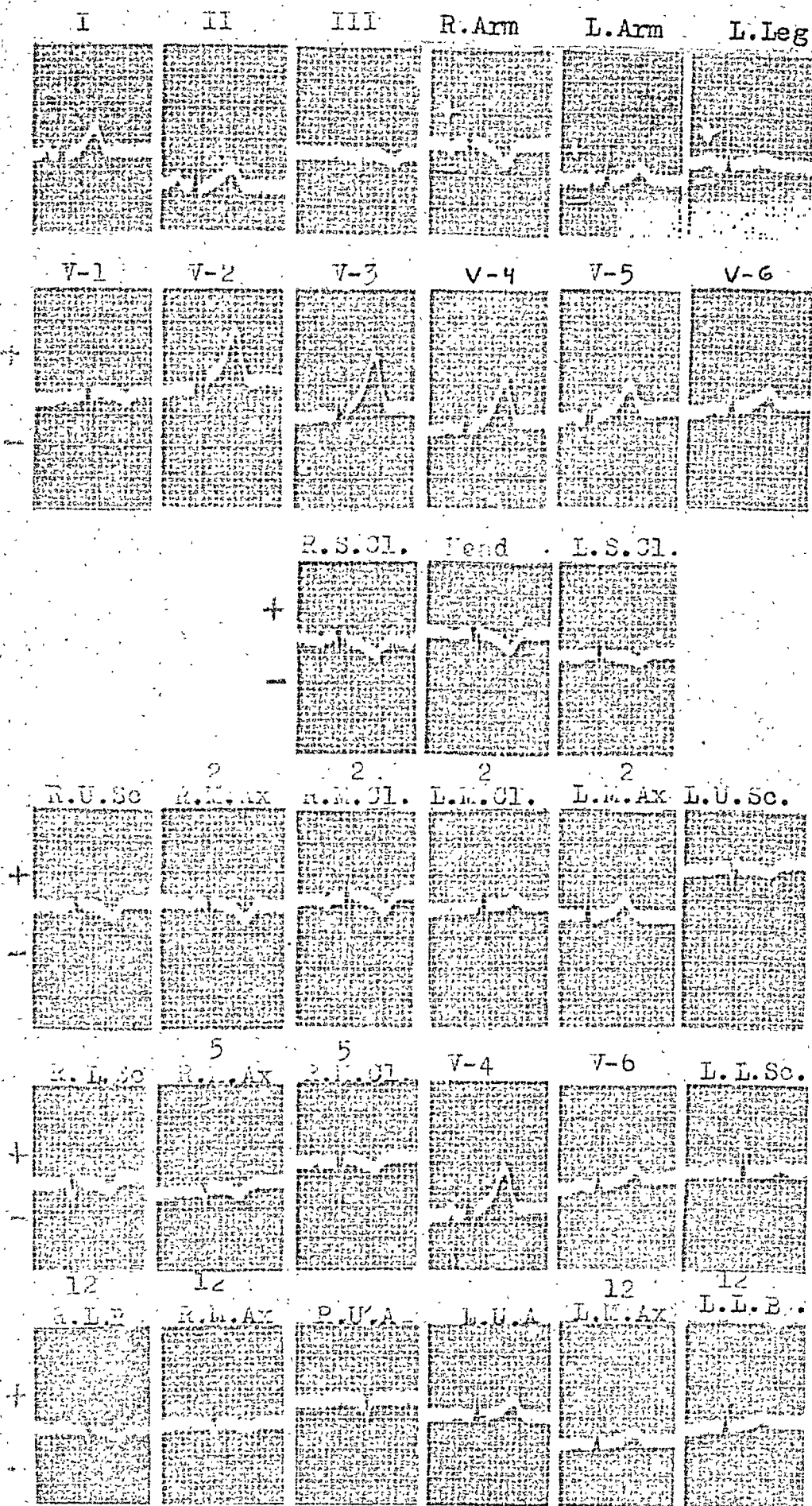
Fig. 3.—H. S., male, 26 years of age, normal.

For descriptions of symbols, refer to the text. The precordial leads V_4 and V_6 are repeated in most of the records. The unipolar leads are so taken that positivity is represented by an upward deflection.

10. 2 L.M.Cl. lead, similar to 2 R.M.Cl. lead.

11. 2 L.M.Ax. lead, similar to 2 R.M.Ax. lead.

12. L.U.Sc. lead, similar to R.U.Sc. lead.

13. R.L.Sc. lead, at angle of right scapula.

14. 5 R.M.Ax. lead, from the fifth intercostal space in the right midaxillary line.

15. 5 R.M.Cl. lead, from the fifth intercostal space in the right midclavicular line.

16. Lead V-1, with the electrode in the fourth intercostal space at the right border of the sternum.

17. Lead V-2, in the fourth intercostal space at the left border of the sternum.

18. Lead V-3, placed on the middle of a line joining the points of electrode application of leads V-2 and V-4.

19. Lead V-4 placed at the left midclavicular line in the fifth intercostal space.

20. Lead V-5, in the fifth intercostal space at the left anterior axillary line.

21. Lead V-6, at the left midaxillary line in the fifth intercostal space.

22. L.L.Sc. lead, at the angle of the left scapula.

23. 12 R.L.B. lead, in the twelfth intercostal space directly under the angle of the right scapula.

24. 12 R.M.Ax. lead, in twelfth intercostal space at right midaxillary line.

25. R.U.A. lead, on the right upper quadrant of the abdominal wall, at the level of the lowest costal cartilages and on the prolongation of the midclavicular line to the abdomen.

26. L.U.A. lead, similar to the R.U.A. lead.

27. L.M.Ax. lead, similar to 12 R.M.Ax. lead.

28. 12 L.L.B.. on the back and similar to 12 R.L.B. lead.

29. On some of the patients the unipolar lead V-e, with the electrode over the xiphoid process, was taken. We found, as Wilson, et al.,[2,a] did, that the patterns in this lead were similar to those of lead V-1 or V-2.

Leads were taken with the patients sitting or in a semirecumbent position. The electrocardiograph was standardized so that a deflection in the record of 1 cm. was equivalent to one millivolt. Exceptions to this are found in the aV- leads, in which, although the electrocardiograph was standardized as usual, a 1.5 cm. deflection equals one millivolt.[5] Also, in taking some of the lower back leads, where the potentials were very small, the string was loosened.

RESULTS

The Normal Heart.—Ordinarily the long axis of the normal heart, "from the base to the apex, runs obliquely from behind, forward, and downward to the left."[13] Normal deviations may occur in two directions, depending on the size and shape of the thorax and the position of the diaphragm. In one type, the long axis of the heart is more or less vertical, whereas, in cases of heavy-chested persons with a high diaphragm, the long axis of the heart is likely to be quite oblique.

With this in mind, and from study of Figs. 1 and 2, the principles described above can be applied, and, on theoretical grounds alone, the following unipolar electrocardiographic patterns can be predicted:

a. Leads from the right arm, right shoulder girdle anteriorly and posteriorly, the head, left shoulder girdle posteriorly, and the right anterior part of the chest, including lead V-1, can be said to face the ventricular cavity. Therefore, the main QRS deflection should be (−).

b. Leads overlying or facing the epicardial surface of the left ventricle, i.e., from the left side of the precordium and left upper abdomen and left lower back should have a (+) main QRS deflection.

c. Leads overlying or facing the epicardial surface of the right ventricle, such as those over the lower midsternal region and right upper abdomen, should also have a (+) main QRS.

d. Transition zones may be expected in those regions which lie at the boundaries of those just described.

e. The T wave should tend to point in the same direction as the QRS.

Actual records correspond well to this, and may be divided into two types, determined by the location of the main transition zones. These zones are in the region of the left arm lead, the R.U.A. lead from the right upper abdominal wall, and the left leg lead.

To consider the left arm lead, we found that, although in all our records the upper left scapular lead was always (−), the left arm lead was either (+), biphasic, or (−) (with occasionally a [−] T), depending on whether the left arm was facing the epicardial surface of the left ventricle or the endocardium, which in turn depended on the position of the heart. When the long axis of the heart is oblique, the left arm lead faces the epicardium of the left ventricle and is therefore (+). With a vertical long axis, the left arm lead faces the endocardial surface of the ventricles and tends to be (−).

The second zone of transition was noted in the R.U.A. lead over the right upper abdominal wall. Here the potentials also varied from (+) to (−) Figs. 3 and 9, a. Although it might seem at first a paradox for a lead from the right upper abdominal wall, which faces the epicardial surface of the right ventricle (it also faces a portion of the left ventricle), to have a (−) QRS, this apparent discrepancy is easily explained when one remembers what was pointed out above, namely, that the electrical activity of the left ventricle is greater than that of the right, and that an electrode, although facing the oncoming (+) wave from within the right ventricle, at the same time is also facing the stronger (−) tail end of the wave passing outward through the main muscle mass of the left ventricle. As will be seen later with cases in which hypertrophy of the right ventricle was present, the patterns in this region of the body approach those theoretically anticipated.

When the heart is oblique the right upper abdominal lead faces more of the right ventricular surface and is (−); when the heart lies vertically the right upper abdominal lead faces more of the lower surface of the left ventricle, and its potential becomes slightly (+) (in children the [+] deflection may be marked).

The potentials of the left leg lead resemble those of the abdominal wall rather than those of the back; their appearance was intermedi-

ate between those of the right and left upper abdominal leads. They are not, therefore, as sensitive an index of the position of the heart as the right upper abdominal lead. Ordinarily the left leg lead faces varying aspects of the epicardial surfaces of both the right and left ventricles, also. With a vertical, normal heart, the left leg lead faces more of the left ventricle than of the right, and its potential is (+). When the normal heart lies obliquely, it faces more of the right ventricle than of the left, and its potential tends to be small and isoelectric, and even downward.

The right arm lead, always facing the endocardium, maintains its (−) potentials. There is, therefore, a reciprocal relation between the potentials of the left arm and left leg leads: When the heart lies vertically, the left leg lead faces the left ventricle and is upright; the left arm lead, facing the endocardium, has a downward potential. When the heart lies obliquely, it is the left arm lead which faces the left ventricle, and is upright; the left leg lead, facing the small right ventricle, is downward.

These results can also be interpreted in terms of standard leads. Although each of the standard leads represents the algebraic difference between the potentials of the two extremities being used,[6, 14] for the purposes of this paper we can state that Lead I resembles the left arm lead and Lead III resembles the left leg lead, especially if Leads II and III are similar. Lead II, of course, equals the sum of Leads I and III.

Therefore, when the long axis of the heart is vertical, the left leg lead, facing the left ventricular surface, and Lead III will be upright; the left arm lead, facing the endocardium, and Lead I will be downward. This pattern has been arbitrarily designated as right axis deviation.

When the long axis of the heart is oblique, it is the left arm lead which faces the left ventricular surface, and it and Lead I will be upright; and the left leg lead, facing the right ventricular surface, and Lead III will tend to be isoelectric or downward. This has been arbitrarily designated as no axis deviation or left axis deviation, respectively.

When the left arm and left leg potentials are about equal, as they often are, Lead III will be isoelectric (Lead III equals the left arm minus the left leg potentials).

To summarize: the electrical axis in the normal electrocardiogram is determined by the position of the heart within the thorax, and, more particularly, by the relations of the left ventricular surface to the left arm and left leg leads. A vertical heart produces the patterns arbitrarily designated as right axis deviation; an oblique heart produces the patterns arbitrarily designated as a normal electrical axis and left axis deviation.

A word may be said about the precordial leads. It can be seen in Fig. 3 that lead V-1 is similar to leads from the right upper chest, and leads V-5 and V-6 are similar to leads from the left upper body anteriorly. Thus, the biphasic leads V-2, V-3, and V-4 may also be considered

transitional leads, although in the normal their patterns do not vary to any extent with variations in the position of the heart.

Left Ventricular Hypertrophy.—When hypertrophy of the left ventricle occurs due to hypertension or other causes, the following factors tend to make the electrocardiogram deviate from normal: (a) The left ventricle enlarges anteriorly, to the left, and posteriorly. With this, the apex is usually displaced both downward and to the left, causing the long axis of the heart to be more oblique than it is normally; (b) The greatly enlarged left ventricle serves to further enhance its dominance of the electrical activity of the ventricles.

With these additional factors in mind, theoretical analysis, similar to that used for the normal heart, allows the following predictions:

1. Because of the marked obliquity of the heart, not only the left arm lead, but leads from the head and supraclavicular regions should tend to face the epicardial surface of the left ventricle, and record (+) potentials instead of being (−).

2. Due to the greatly enlarged left ventricle and its increased electrical activity, leads from a large area of the left upper portion of the trunk facing the left ventricle should exhibit large (+) potentials and the standard leads should also have large amplitudes; leads facing the epicardial surface of the right ventricle (and consequently the endocardium of the left ventricle) should be definitely (−). Actually, these conditions prevail (Figs. 4 and 5).

In Fig. 4, from a 73-year-old white man with hypertension, although the right arm lead (aVr lead) shows a (−) potential, in the right supraclavicular region (R.S.Cl. lead) the potential is biphasic and partly (+), and it is (+) at the head and at the left supraclavicular region (L.S.Cl. lead). Leads from the left upper trunk anteriorly and posteriorly, including the L.U.Sc. lead from the base of the spine of the left scapula, also have a (+) potential. All the leads from the right side of the body, anteriorly and posteriorly, on the other hand, have a (−) main QRS.

It should be noted that leads from the left abdominal wall, angle of the left scapula, and left lower back have a (−) main QRS. This is further indication of the marked obliquity of the heart, and of the fact that the main muscle mass of the hypertrophied left ventricle now points posteriorly in the direction of the left shoulder girdle, rather than inferiorly. Therefore, with leads from the lower left side of the trunk and the left leg, the main body of the wave of activation will be moving away from them, and QRS will be (−), even though the wave is passing outward to the epicardium.

The precordial leads are very characteristic. Those near the sternum are like leads from the right side of the body, and those near the apex are like those from the left side of the body. Changes in the RS-T segment and T wave can be better analyzed in the following record, Fig. 5, from a 48-year-old white woman with a blood pressure of 250/150.
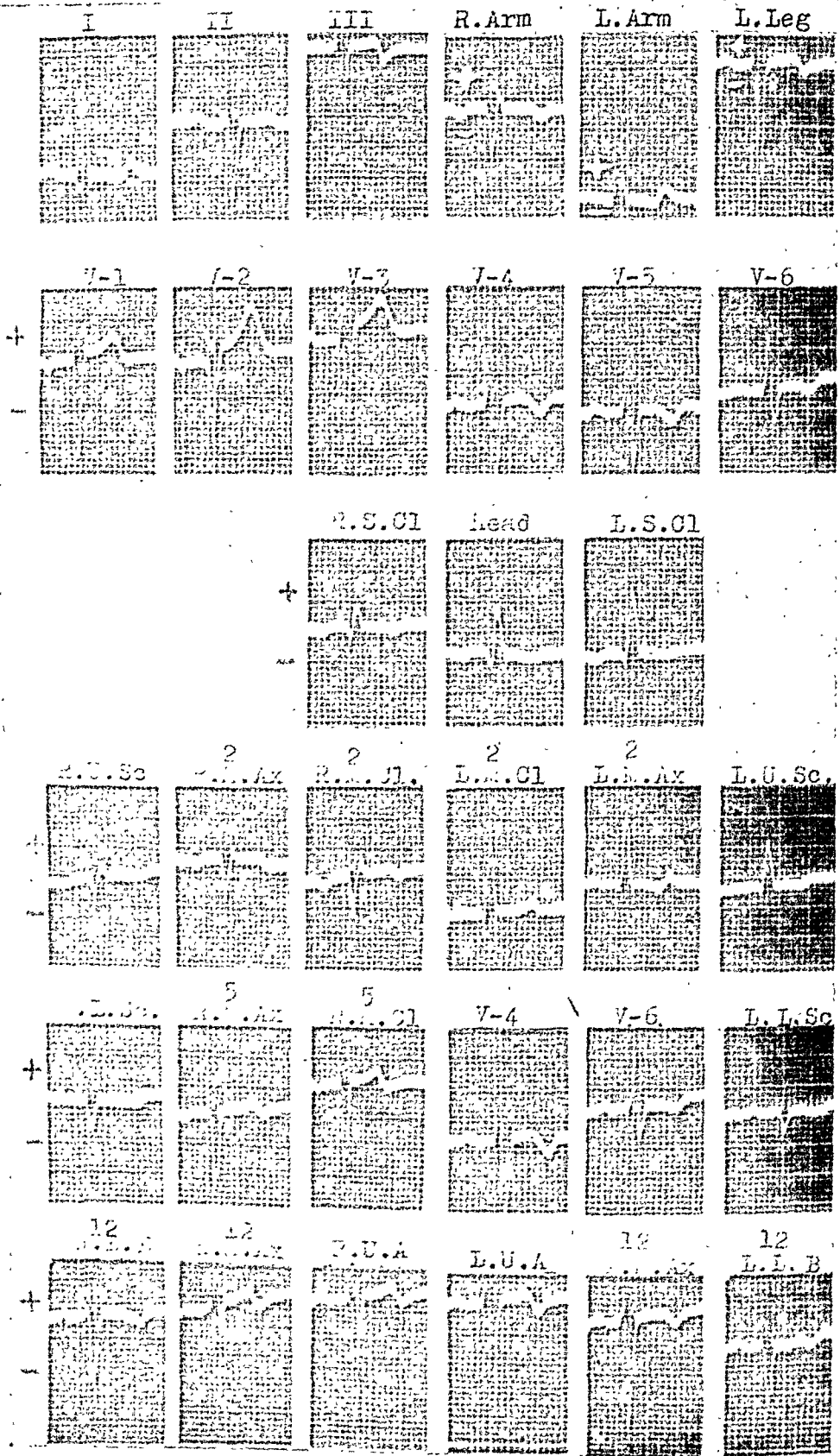
Fig. 4.—M. Z., male, 72 years of age, hypertensive cardiovascular disease. Patient had no complaints referable to the heart, and was receiving no medication.
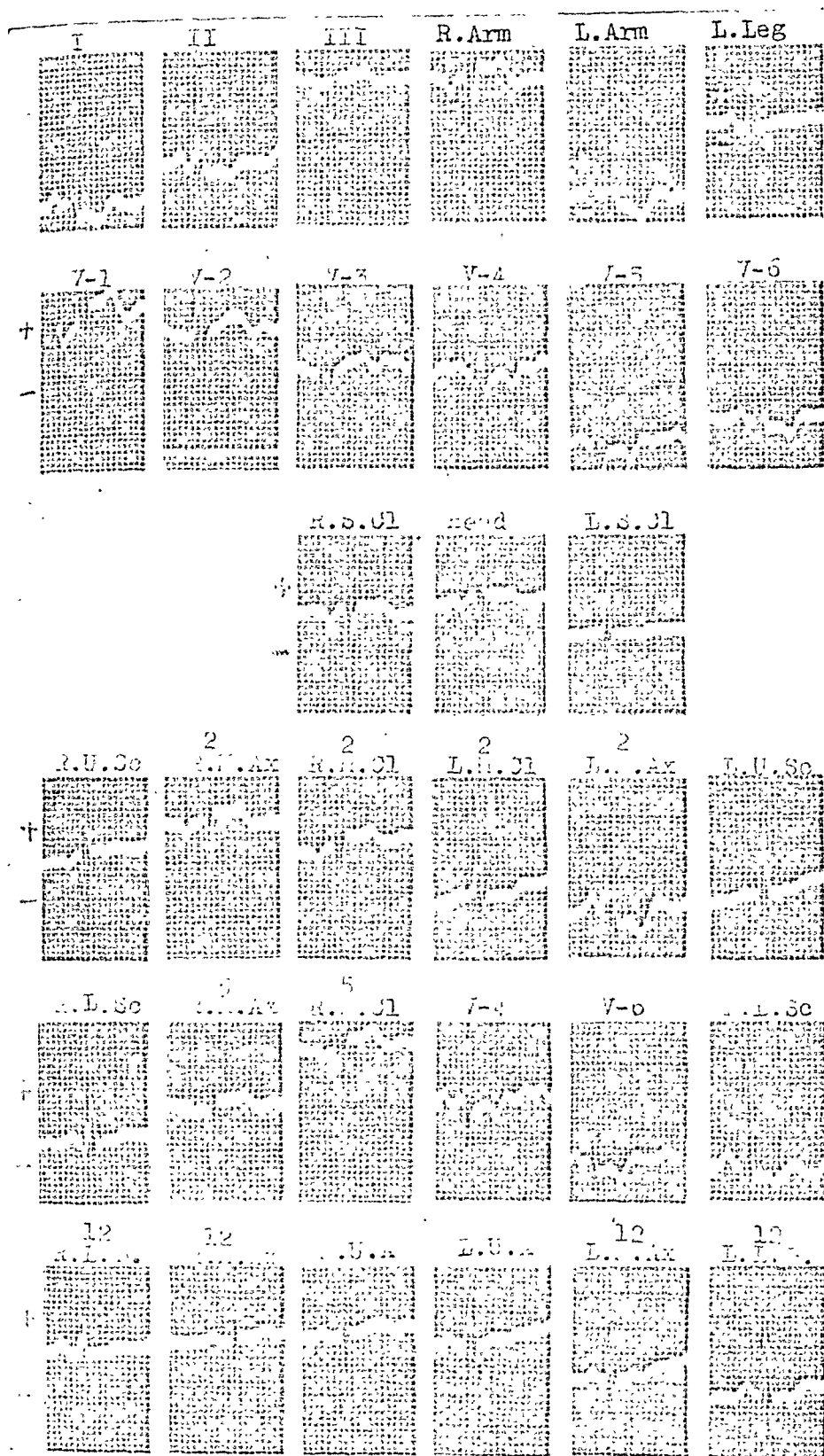
Fig. 5.—M. G., female, 48 years of age, hypertensive cardiovascular disease. Blood pressure, 250/150; no medication given.

One perceives that the T wave in practically all the leads points in a direction opposite to that of the QRS, and that, along with this, the RS-T segment is no longer isoelectric, but has also deviated in a direction opposite to the QRS. Although many reasons for this have been proposed,[15, 16] an adequate explanation is not yet available other than that the changes do not indicate myocardial damage. A more detailed interpretation of these changes will be presented in another paper.[23]

In this case the QRS patterns are, in the main, similar to those in Fig. 4. Here the long axis of the heart is less oblique, and although the left supraclavicular lead (L.S.Cl. lead) has become (+), the head and R.S.Cl. leads remain (–). Posteriorly, leads from the right lower back and all the leads from the left side of the back are (+), which is also a sign that the obliquity of the heart is less than in the case illustrated in Fig. 4.

Fig. 8 represents another interesting case in which marked left ventricular hypertrophy was present in association with right ventricular hypertrophy. Note the presence of right axis deviation in spite of the left ventricular hypertrophy which was present.

The extremity leads, as in the normal, occupy transition zones of potential, and variations are due to the position of the heart in the chest and *not* primarily to the left ventricular hypertrophy. Usually, the heart lies obliquely, and this, as in the normal, results in left axis deviation. However, because the obliquity is more marked than normal, the left leg lead, facing the right ventricle, becomes deeply (–). The right arm potentials usually remain (–), although, with marked shift of the long axis, these too become biphasic. It is this, as has been previously reported,[6] which is the cause of the two types of patterns in left ventricular hypertrophy which Barnes has described.[15] In the first type, the right arm lead is (–), and Leads I and II are similar; when the right arm becomes biphasic, Leads II and III become similar.[*] Figs. 4 and 5 illustrate these two types.

When due to other factors, such as abnormalities of the thoracic cage, concomitant enlargement of the right ventricle, etc., the long axis of the heart tends to remain vertical, and the extremity leads will show the normal patterns, without axis deviation, in spite of the ventricular hypertrophy. In such cases, however, the characteristic (+) QRS in leads over the hypertrophied left ventricle, and the (–) QRS in leads facing the right ventricle, along with high voltage in the standard leads and RS-T and T-wave changes, are often observed.

Cases of left ventricular hypertrophy have been described which show only marked left axis deviation.[†] In our cases of this type, the marked obliquity of the heart produced not only the patterns of left axis deviation, but, because of the large left ventricle, the left upper scapular lead (L.U.Sc. lead), which in the normal is always (–), had become

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[*] This may also occur in a markedly oblique normal heart.
[†] A downward Lead II and III.

(+)* (Fig. 9, b). To summarize, then, the main features of the patterns in hypertrophy of the left ventricle are:

1. The QRS in leads over the hypertrophied left ventricle, particularly the precordial leads V-4, V-5, and V-6, are large and (+), and high voltage in the standard leads is often observed.

2. Leads facing the small right ventricle, such as the precordial leads V-1 and V-2 and the R.U.A. lead from the right upper abdominal wall, are (−).

3. With this may be associated characteristic RS-T and T-wave patterns in which they deviate in a direction opposite to the QRS.†

4. The unipolar extremity and standard leads may exhibit left axis deviation or normal or even right axis deviation, depending on the long axis of the heart, just as in the normal. Usually the long axis of the heart is quite oblique, and left axis deviation is present (high left arm and Lead I potentials, and deep left leg and Lead III potentials). When the obliquity is very marked, Lead II also points downward.

5. In cases in which the obliquity of the long axis of the heart causes left axis deviation without RS-T and T changes, the left ventricular hypertrophy causes the entire left shoulder girdle, including the left upper scapular lead (L.U.Sc. lead), to be (+). This does not occur in the normal oblique heart.

Right Ventricular Hypertrophy.—With right ventricular hypertrophy the following factors tend to make the electrocardiogram deviate from normal:

a. With moderate right ventricular hypertrophy there may not be any apparent change in the contour and position of the heart.[24, 25] With marked enlargement, the right ventricle bulges anteriorly, obliterating the retrosternal space, and the apex of the heart is displaced horizontally to the left. Occasionally there occurs the so-called triangular heart.[24] The effect of this on the long axis of the heart is variable, but it usually remains more or less vertical.

b. The increased mass of the right ventricle tends to counterbalance the electrical activity of the left ventricle. Thus, again on theoretical analysis, the following unipolar patterns may be predicted:

1. Because of the vertical long axis of the heart, leads from the head and both shoulder girdles should be (−), and right axis deviation should be present, as in the normal vertical heart.

2. Leads facing the epicardial surface of the hypertrophied right ventricle, such as those over the right lower anterior part of the chest and midsternal region, and both sides of the abdominal wall, should have a (+) QRS.‡ Study of actual records confirms this.

Fig. 6 is a record from a 43-year-old white woman with an interauricular septal defect and mitral stenosis (Lutembacher syndrome).

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*See *Appendix*.

†The undulating RS-T and T may be likened to a roller coaster. The presence of this pattern does not necessarily indicate ventricular hypertrophy.

‡The vertical position of the heart also contributes to the (+) abdominal wall potentials.

She had mild decompensation, for which she had been digitalized. Note the (+) main QRS deflections in leads from the lower right anterior chest and right upper abdomen, and the (−) QRS from leads from the head, left upper chest, and both shoulder girdles.

In the precordial leads, the (+) potential of lead CF_2 is typical. Usually the first precordial lead (here CF_1 with the left leg as the indifferent electrode) also has a large (+) deflection, but in this case it resembled the other leads from the right upper anterior chest wall. This, however, may be due to the effect of the potentials of the left leg.

Over the left side of the precordium, as lead V-6, the potentials from the right and left ventricles tend to balance each other, and a biphasic complex is recorded. When the left ventricle is small compared to the right ventricle, the leads over the left side of the precordium, facing the tail end of the wave passing outward through the large ventricle, will record (−) deflections as in leads from the left shoulder girdle. In this case, digitalis probably contributed somewhat to the RS-T and T deviations[17] which, however, are often observed with right ventricular hypertrophy.*

In the extremity leads, because of the vertical long axis of the heart, the left arm lead faces the endocardium and is consistently (−). The right arm lead usually is (−), but when the long axis of the heart is very vertical, the right arm tends to face the epicardium of the right ventricle as well as the endocardium, and becomes biphasic. It is this, as has been previously reported,[6] which is the cause of the two types of patterns in right ventricular hypertrophy which Barnes has described.[15] In the more common type, the right arm is (−) and Leads I and II are similar. When the right arm lead becomes biphasic, Leads II and III become similar (Figs. 6 and 9, d).

Because of the vertical position of the heart, the left leg might be expected to face the epicardium of the left ventricle as in the normal vertical heart. If the left ventricle is small compared to the right ventricle, the left leg lead, which faces the left ventricle, will tend to be isoelectric. This, as Wilson and his associates[3a] have pointed out, results in deep S waves in the three standard leads, rather than right axis deviation. An example of this is shown in Fig. 9, e.

Isolated right ventricular hypertrophy is, however, much less common than cases in which there is concomitant hypertrophy of both the right and left ventricles. In fact, it has been stated that the most frequent cause of right ventricular hypertrophy is an antecedent hypertrophy of the left ventricle.[26] In such cases, the electrocardiographic patterns are not as characteristic as the one just described.

Fig. 7 illustrates such a case, that of an 80-year-old white woman with emphysema and hypertension. She was not receiving any medication. Note how the features of both right and left ventricular hypertrophy are present. The precordial leads are suggestive of left ven-

*Here again, the presence of the RS-T and T changes does not necessarily indicate ventricular hypertrophy.

tricular hypertrophy. But the downward T_2 and T_3 are usually seen with right ventricular hypertrophy,[18] as are the (−) potentials of the head and both shoulder girdles and the (+) QRS and (−) T of the R.U.A. lead from the right upper abdominal wall. In this connection, an important fact should be noted: In all our cases of right ventricular hypertrophy, the R.U.A. lead from the right upper abdominal wall
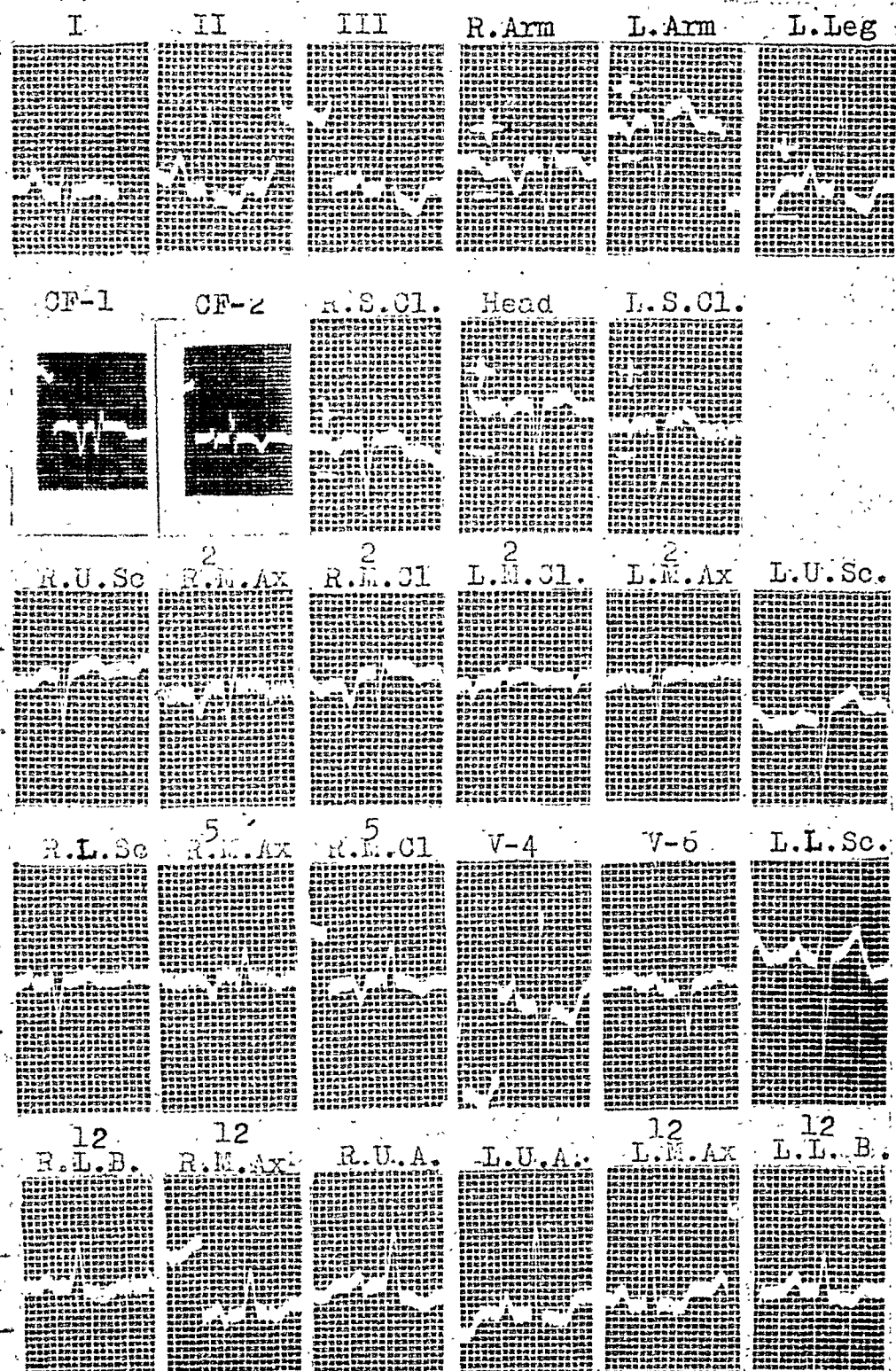
Fig. 6.—P. B., female, 43 years of age, interauricular septum defect and mitral stenosis (Lutembacher syndrome). Patient had mild decompensation, for which she had been digitalized. Photographs of the precordial leads CF₁ and CF₂, taken with the leg as the indifferent electrode, are included.
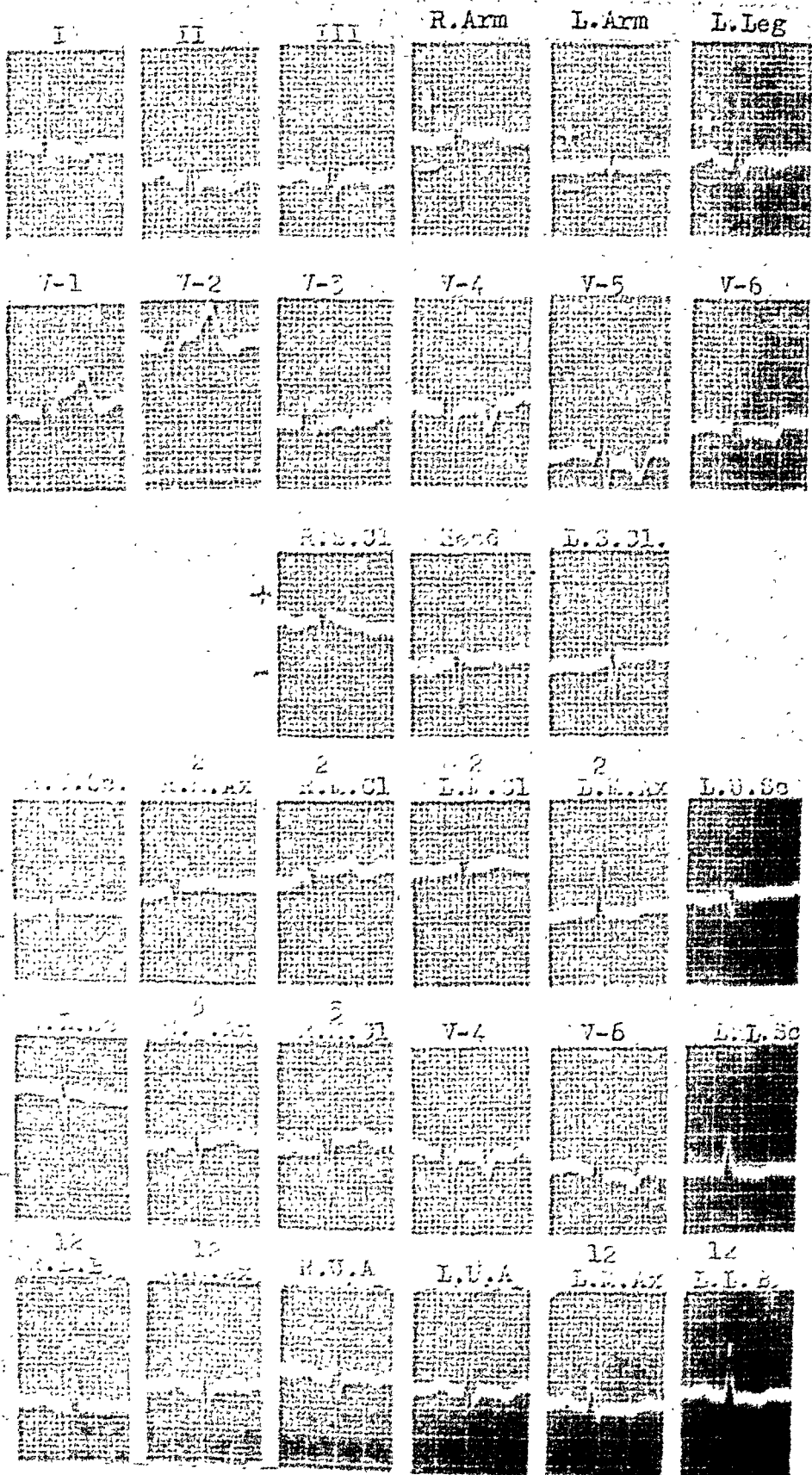
Fig. 7.—T. A., female, 80 years of age. Emphysema and hypertensive cardiovascular disease. Patient was not receiving any medication.
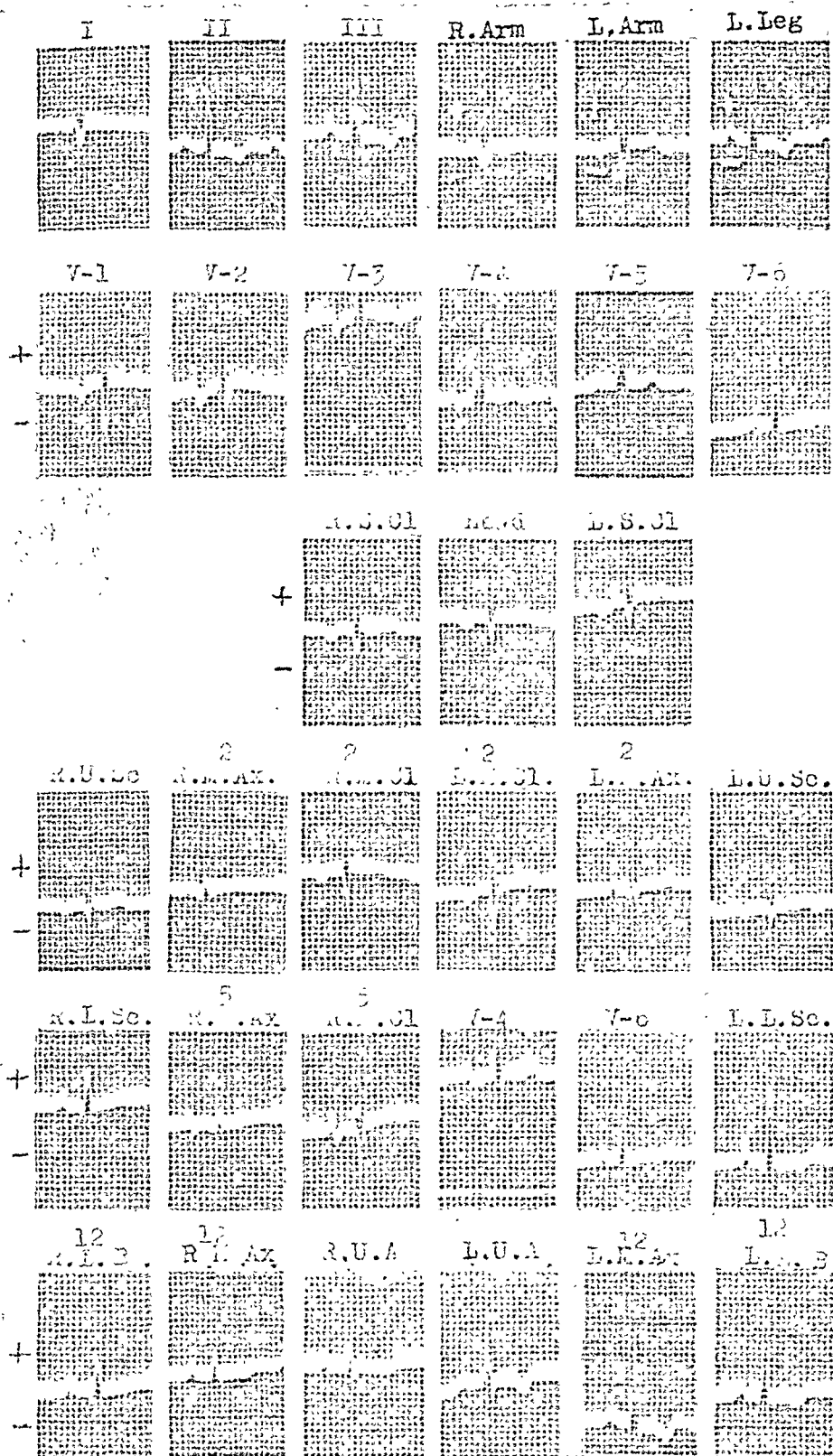
Fig. 8.—C. D., colored, male, 45 years of age. Hypertensive cardiovascular disease and kyphoscoliosis, and latent syphilis. Patient had moderate right heart failure, for which he had been digitalized. Blood pressure, 180/125.

was (+), irrespective of whether left ventricular hypertrophy was or was not present. In all our cases of isolated left ventricular hypertrophy, this lead was (−) or isoelectric.

Cases of right ventricular hypertrophy have been described in which there was only right axis deviation without RS-T and T-wave changes. In our cases of this type, the vertical, long axis of the heart produced

I	II	III	R.Arm	L.Arm	L.Leg	V-4	RUA	LUSc
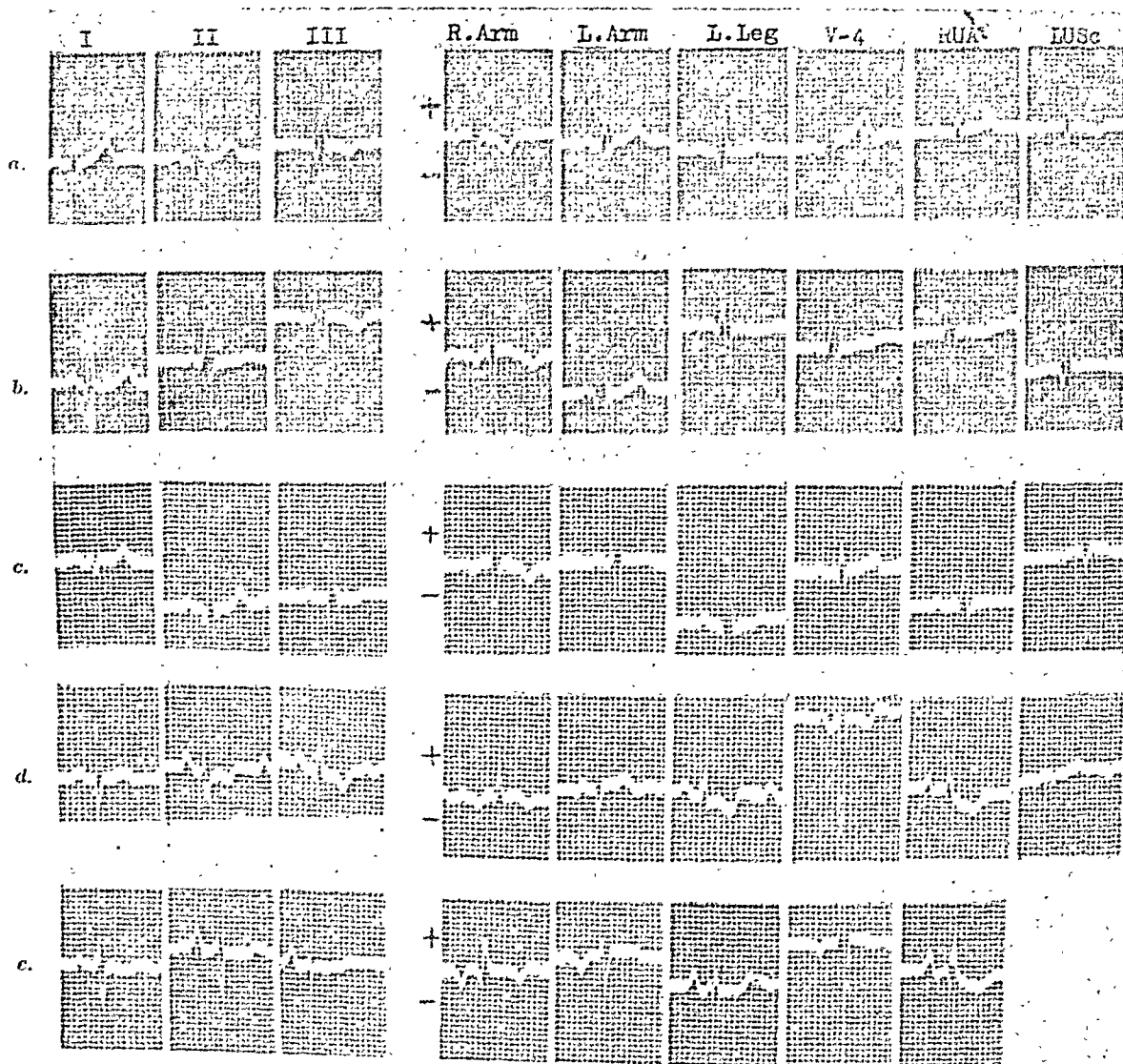
Fig. 9.—a, J. J., male, 26 years of age, normal; b, R. W., female, 46 years of age, hypertensive cardiovascular disease; c, R. G., female, 41 years of age, chronic fibroid pulmonary tuberculosis; d, E. C., female, 48 years of age, chronic asthma; and e, B. K. male, 59 years of age, chronic cor pulmonale (the precordial lead is CF4).

not only the pattern of right axis deviation (deep left arm and Lead I potentials, and high left leg and Lead III potentials), but, because of the large right ventricle, the R.U.A. lead from the right upper abdominal wall, facing the right ventricle, had become highly (+), which is not observed normally[*] (Fig. 9, c).

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*See Appendix.

To summarize, right ventricular hypertrophy may cause the following electrocardiographic patterns:

1. Leads facing the enlarged right ventricle, especially the R.U.A. lead from the right upper abdominal wall, are characteristically (+). A (+) QRS is also often observed in precordial leads from the midsternal region, and standard leads may also have high voltage.

2. Leads from the left side of the precordium, facing the left ventricle, are biphasic and may be (−) if the left ventricle is comparatively small.

3. With this, there are often associated RS-T and T-wave deviations in a direction opposite to the QRS.

4. The unipolar extremity and standard leads may exhibit right axis deviation, or no axis deviation, or deep S waves in the three standard leads,* depending on the long axis of the heart. Usually the heart is vertical and, as in the normal, the left leg lead faces the epicardial surface of the left ventricle and the left arm lead, the endocardium, producing deep left arm and Lead I potentials and high left leg and Lead III potentials (right axis deviation).

5. The presence of left ventricular hypertrophy in association with the right ventricular hypertrophy causes variations in the long axis of the heart (and therefore changes in axis deviation), and the precordial leads resemble those observed in uncomplicated left ventricular hypertrophy. However, in such cases, as well as in cases in which the hypertrophied right ventricle causes changes in axis deviation only, the right upper abdominal lead (R.U.A. lead), which faces the right ventricle, is always (+), indicating the presence of hypertrophy of the right ventricle.

DISCUSSION

The principle of considering the electrical activity of the heart as a whole is essentially that developed by Wilson and his associates some years ago.[7, 8] However, the fact that leads taken with the exploring electrode on the exposed surface of the heart (direct leads), or over a saline soaked gauze pad overlying the heart (semidirect leads), or on the thorax over the heart give records which are qualitatively similar, except that the amplitude of the deflections decreases as the electrode is moved farther from the heart, have led them to postulate the concept that precordial leads preferentially depict events in that region of the heart immediately underlying the electrode, that the main (−) deflection of the QRS complex begins when the muscle underlying the electrode becomes activated, and that the patterns of axis deviation depend on whether the potentials from the epicardial surfaces of the right ventricle and left ventricle are transmitted to either the left arm and left leg respectively, or vice versa.

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*Left axis deviation will not occur even if the heart is oblique because the left leg lead, facing the large right ventricle in such a case, will be upright instead of small.

We feel that this explanation is too limited in scope, however. In the first place, the distance from the surface of the right and left ventricles to the chest wall is sufficiently great to minimize the effects of any one small area of the heart on the electrode. Secondly, the orderly sequence of unipolar lead patterns over the entire surface of the body, and the similarities between precordial leads and leads from adjacent regions of the chest appear to indicate that one mechanism is responsible for all the patterns. If this is not so, at what point does the electrode cease favoring selective potentials from the underlying muscle, and begin to record the electrical activity of the ventricles as a whole?

With respect to Groedel's ideas[19] about partial thoracic electrocardiograms in which he claims to have isolated the electrocardiograms from the right and left ventricles, the criticism leveled at the above concepts more strongly apply. Furthermore, our records do not support Groedel's ideas.

The concepts of Katz and his associates,[20, a, b] in which complex batteries spread throughout the ventricles, is unnecessarily complex, we think.

Although we have emphasized the changes in axis deviation in terms of shifts in the long axis of the heart around an anteroposterior axis, experimental observations have shown that, in the normal, there occurs, along with the shift in the long axis, concomitant rotation of the ventricles around the long axis.[*] The relations between the changes in the long axis and the direction of rotation of the ventricles around the long axis are usually constant. Thus, when the long axis of the heart becomes more vertical, the anterior surface of the right ventricle tends to rotate to the left; and when the long axis becomes oblique, rotation of the right ventricle is to the right.[22]

CONCLUSIONS

The following principles, which serve to explain the electrical activity recorded from a simple muscle strip, are applicable to the study of the electrical activity of the human heart as recorded by unipolar and standard leads.

1. When the electrical activity of the heart is studied with multiple unipolar leads on the surface of the body, the electrocardiograms obtained are observed to vary in an orderly sequence. These variations are dependent on: (a) the location of the electrode, (b) the size, shape, and position of the ventricles, (c) the direction in which the wave of activation spreads in the muscle, and the direction of the regression wave, and (d) the distance of the electrode from the source of electrical activity.

2. Irrespective of the location of an electrode on the surface of the body, it records potentials from the both ventricles, rather than preferentially recording potentials from any one area of the heart.

*There may also be rotation around a transverse axis and perhaps other axes.

3. In the human heart, which resembles an asymmetrical cup with its open end facing the head and right shoulder girdle, the spread of electrical activity is from within outward, in both ventricles. However, since the mass of the left ventricle is greater than the right, its electrical activity tends to dominate the electrocardiogram.

4. The unipolar electrocardiogram depends, therefore, primarily on the relation of the electrode to the endocardium or the epicardium; and if the electrode faces the epicardium, the relative sizes of the ventricles must also be taken into account.

5. In the normal heart, leads from the right upper region of the body, including the right arm lead and the precordial lead V-1, face the endocardium, and are (−). Leads facing the epicardium of the left ventricle, as precordial leads V-5 and V-6, are (+). The left arm lead, the left leg lead, and the right upper abdominal wall lead are situated in transitional zones of potential, however. The polarities of these leads often vary greatly with changes in the long axis of the heart.

When the heart lies vertically, the left leg lead faces the surface of the left ventricle, and its potential, as well as that of Lead III, which resembles it, is upward. The left arm lead faces the endocardium, and it and Lead I, which resembles it, are downward. This pattern has been arbitrarily designated as right axis deviation.

When the heart is oblique, it is the left arm lead which faces the left ventricular surface. Therefore, it and Lead I are now upright. The left leg lead faces the right ventricular surface, and it and Lead III tend to be small or even downward. The pattern has been arbitrarily designated as that of a normal electrical axis or of left axis deviation, depending on whether Lead III is upright or downward.

It may therefore be said that the relations of the surface of the left ventricle to either the left arm lead or the left leg lead govern the patterns known as axis deviation.

7. Because the paths of activation and of regression of the electrical activity in the normal heart are different, the T wave points in the same direction in practically all unipolar leads.

8. When hypertrophy of the left ventricle occurs, the obliquity of the heart causes the patterns of left axis deviation, just as in the normal. However, the left axis deviation is often marked (Lead II, as well as Lead III, is downward). Also, in such cases, because of the hypertrophy of the left ventricle, the left upper scapular lead (L.U.Sc. lead) becomes (+).

If for any reason the long axis of the heart becomes or remains vertical, normal or even right axis deviation may be seen. Along with the changes in axis deviation, RS-T and T deviations in a direction opposite to the QRS are often seen in practically all leads, although the presence of the RS-T and T deviations does not necessarily indicate ventricular hypertrophy. Along with this there may be the following additional signs of enlargement of the left ventricle: large (+) deflections in leads facing the hypertrophied left ventricle, as from the left

side of the chest, especially precordial leads V-4, V-5, and V-6, and high voltage in the standard leads; and deeply (−) deflections in leads facing the small right ventricle, as from over the midsternal region and the right upper abdominal wall (R.U.A. lead).

9. With hypertrophy of the right ventricle, the heart tends to lie vertically and right axis deviation occurs as in the normal. If the left ventricle is small compared to the right, the left leg lead, facing the left ventricle because of the vertical position of the heart, will also be small in amplitude. This may result in deep S waves in the standard leads, rather than the pattern of right axis deviation. There may also be RS-T and T deviations in practically all leads (although, here again, their presence is not necessarily an indication of ventricular hypertrophy), and the following additional signs of enlargement of the right ventricle: (÷) deflections from leads facing the hypertrophied right ventricle, such as the right upper abdominal lead (R.U.A. lead), and often the precordial leads from the midsternal region; and biphasic, small, or even downward deflections from leads over the left side of the chest, which face the small left ventricle.

When there is concomitant left ventricular hypertrophy, the precordial leads record the characteristics of the left ventricular hypertrophy. The right upper abdominal lead, facing the hypertrophied right ventricle, however, is (÷) even in such cases.

To conclude, when the normal and hypertrophied heart is studied by means of unipolar leads taken over the surface of the entire body, it becomes evident that, although leads near the heart and from the right shoulder girdle have a fairly fixed pattern, the left arm and left leg leads occupy transition zones of potential, and the unipolar extremity and standard leads are influenced not so much by the size of the heart as by its position in the thorax. It is for this reason that chest leads offer a more suitable index of ventricular hypertrophy than the extremity leads. However, the multiple precordial leads in use today are only partially successful in recording evidence of right ventricular hypertrophy, especially when it is associated with some degree of left ventricular hypertrophy. Our incidental observation of the constancy of the pattern of the right upper abdominal unipolar lead, particularly in such cases, makes us suggest that it may have use as an index of right ventricular hypertrophy. Similarly, the left upper scapular unipolar lead may have value in diagnosing left ventricular hypertrophy when only left axis deviation is present in the standard and precordial leads.

SUMMARY

1. The physiologic principles by which unipolar leads can be interpreted are described.

2. The patterns of unipolar surface potentials over the body in the normal subject and in cases of right and left ventricular hypertrophy are illustrated.

3. A nonmathematical approach to the problem of axis deviation is presented.

4. The advantage of leads close to the heart over extremity leads in the diagnosis of ventricular hypertrophy is emphasized.

5. The use of the right upper abdominal unipolar lead (R.U.A. lead) as an index of right ventricular hypertrophy, and of the left upper scapular unipolar lead (L.U.Sc. lead) in the diagnosis of hypertrophy of the left ventricle is briefly described.

APPENDIX

Our observations on the use of the right upper abdominal and left upper scapular unipolar leads have not been confined to the small series of cases described in this paper. We have begun to collect a large series of these leads in order to establish exact standards for their values. Judging from our preliminary observations, an amplitude of more than (+) or (−) 4 mm. in an adult is to be considered abnormal. We have not as yet developed standards for children, in whom the amplitudes of these leads are larger than in adults.

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ADDENDUM

Although study of Fig. 1 led us, at first. to think that the T-wave changes often observed in cases of ventricular hypertrophy were indicative of the fact that the paths of activation and of regression were now similar. we no longer believe that this is the only explanation possible. Recent observations of ours which have been made since this paper was written[23] suggest that. in some of the cases of ventricular hypertrophy in which T-wave changes are present, they are due not to the hypertrophy but to the position of the heart, in a manner similar to that affecting the QRS complex. Thus, when the heart is vertical and markedly rotated clockwise around its long axis, a downward T_2 and T_3 may occur, along with the high QRS $_{2 \text{ and } 3}$, because of the position of the heart. even if it is normal in size. Similarly, we feel that an oblique heart, with marked, counterclockwise rotation around its long axis. irrespective of its size. may cause a downward T_1 in addition to the high QRS_1.

In other cases. the changes in the RS-T segment and the T wave may be due to the large area of the QRS complex. which is so often present in cases of ventricular hypertrophy. These suggestions, however, obviously do not cover all the possible mechanisms which can produce a downward T wave in the absence of myocardial damage. A more complete discussion of the above concepts, impossible in this paper. will be presented elsewhere.[23]

THE VALUE OF ROENTGENOLOGIC EXAMINATION OF THE HEART

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R OENTGENOLOGIC examination of the heart provides data regarding size, shape, and pulsation, as well as relationship to adjacent structures. The present report proposes to review critically the significance in the clinical diagnosis of cardiac disease of data obtained by conventional roentgenologic examination.

In order to make a diagnosis, it is essential to know the size of the heart. It is estimated with much greater accuracy roentgenologically than by percussion or palpation. In so-called normal persons, a fairly uniform correlation is found between the area of the posteroanterior projection and the height and weight.[1] Although a heart that is judged to be enlarged from "prediction" tables must be considered as likely to be diseased, a variation from the average can be anticipated regularly in normal subjects, so that deviations must be evaluated in terms of other clinical data. It must be borne in mind constantly that normality as a statistical concept refers only to average values. Furthermore, significant disease may exist in spite of so-called normal measurements. Indeed, the range about the average values is sufficiently large and the influence of the position of the diaphragm is of such importance that, in experienced hands, precise measurements are an unnecessary refinement, and may be reserved for actuarial or experimental purposes. Usually the experienced observer can compare the size of the heart to body habitus with sufficient accuracy by inspecting the teleoroentgenogram or the orthodiagram. Many observers are satisfied with simple fluoroscopic examination, although this requires greater discrimination.

The shape of the heart does not lend itself easily to classification. Although the terms "mitral configuration" and "aortic configuration" are still used, they have a place only when no diagnostic connotation is implied. More precision in the description of shape is obtained by considering the separate segments of the cardiac contour. Ordinarily, in the posteroanterior projection, for example, it is possible to identify five landmarks. On the right side the cardiac border joins above with the supracardiac segment and below with the diaphragm. On the left side the points are not as sharply defined. Below, there is a rounded nose just above or below the outline of the diaphragm which is described as the roentgenographic apex of the heart. More cephalad is a point on

either side of which the pulsations are opposite: when the contour below contracts, the one above distends. The two segments may be immediately adjacent or may be separated from each other by a segment which pulsates less vigorously or appears still. In most cases these dividing points do not represent constant anatomic landmarks on the cardiac chambers. Comparison with post-mortem material and particularly with the angiocardiographic appearance shows clearly that they are more or less accidental points, where the projected chambers overlap. Hence, measurements made between these points cannot have any anatomic significance. This statement applies to the cardiac contour in all positions of the patient. Precision measurement of the individual chambers, therefore, cannot be attained, but experience does result in a certain visual dexterity in the examination of the contours between these points when correlated with body habitus, the position of the diaphragm, and the size of the heart as a whole. As an aid in the evaluation of these contours we shall present an analysis of the cardiac contour in the normal subject and in those diseases in which there is predominant enlargement of a single chamber. The analysis will be based largely upon angiocardiographic studies, confirmed, however, in most instances by post-mortem correlation.

NORMAL

In a normal person (Figs. 1A, 1B, 1C, and 1D), in the posteroanterior position, the right heart border is made up by the right auricle. At its junction with the supracardiac segment there is ordinarily some part of the ascending aorta. The aortic valve is situated at a variable distance within the shadow of the heart. The lower left contour is constituted by the left ventricle. The segment above this is made up by the pulmonary artery, the contour of which, however, usually is separated from the left ventricular contour by a short segment which does not opacify in the usual angiocardiogram, and most likely represents the left auricular appendage. The pulmonary valve also is hidden in the shadow of the heart. The pulmonary conus, which is the part of the right ventricle adjacent to the valve, does not form a part of the cardiac contour. In a few cases the descending branch of the left pulmonary artery may be projected so that its shadow merges with that of the pulmonary artery, and actually forms the contour of the middle left cardiac segment. As the subject is rotated into the right anterior oblique position, the pulmonary artery becomes the entire middle left arc. Only as the right lateral position is approached does the pulmonary conus also come into contour below the pulmonary artery. Since it is part of the right ventricle, its contraction is ventricular in phase, and is differentiated from the pulsation of the pulmonary artery above it, but not from the contraction of the left ventricle below it. In the left anterior oblique position the right ventricle may constitute part of the most caudad anterior contour in some cases. Angiocardiographic study suggests, however,

that most often the latter is obscured by the right auricular shadow. The lower left border in this position is made up by the left ventricle. There is no way to identify the boundaries of the right ventricle in this view. The so-called interventricular groove which is thought by some to be demonstrable in deep inspiration does not correspond to the position of the interventricular septum as seen angiocardiographically.[2]

POSTERO-ANTERIOR

CODE

LEFT AURICLE   RIGHT AURICLE

LEFT VENTRICLE   RIGHT VENTRICLE
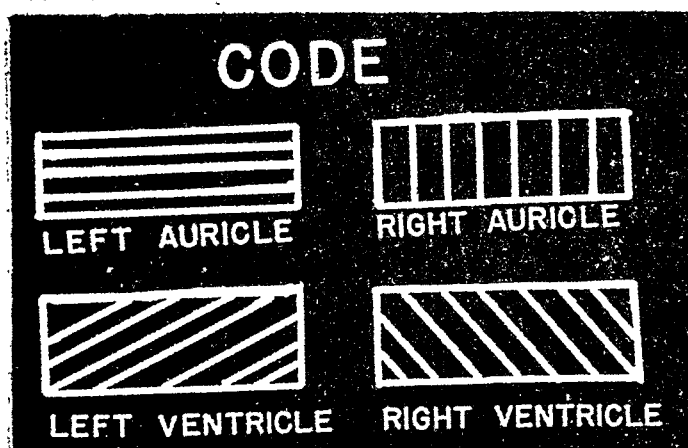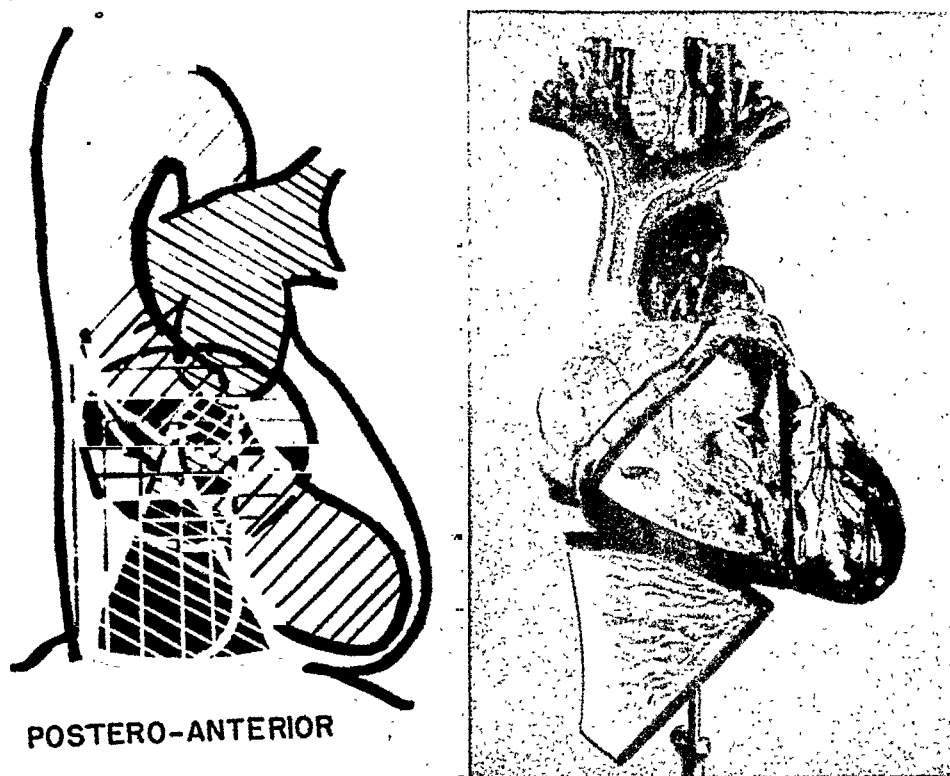
Fig. 1A.—Analysis of the cardiac contours based upon angiocardiograms compared with a model of the heart rotated into a corresponding position. Posteroanterior view. (Right ventricle open.)

In the absence of calcification there is no way to establish the position of the cardiac valves, and any geometric patterns which may be traced through arbitrarily defined points have no anatomic counterparts.

PREDOMINANT ENLARGEMENT OF THE RIGHT VENTRICLE

The right ventricle is enlarged characteristically in cor pulmonale. Even in this condition, the case for study must be chosen carefully to

avoid a confusing left ventricular dilatation due to coronary sclerosis or hypertension. In the suitable case, when the right ventricle is the only chamber significantly enlarged, in the posteroanterior view the heart is found to be widened mainly to the left, and there is a prominence of the pulmonary artery segment of the middle left contour. The cardiac enlargement is seen also in the left oblique position, where, particularly, the portion of the heart merging with the shadow of the diaphragm is widened without protruding into the retrocardiac space. Analysis of the angiocardiograms shows that prominence of the pulmonary artery segment actually is due to dilatation of the pulmonary artery, which, in addition, is elevated above the usual position of this vessel.[3] Apparently, the elevation results from the fact that the right ventricle, which is dilated in all diameters, raises the artery above it. The artery also becomes tortuous, which tends further to exaggerate its convex contour.
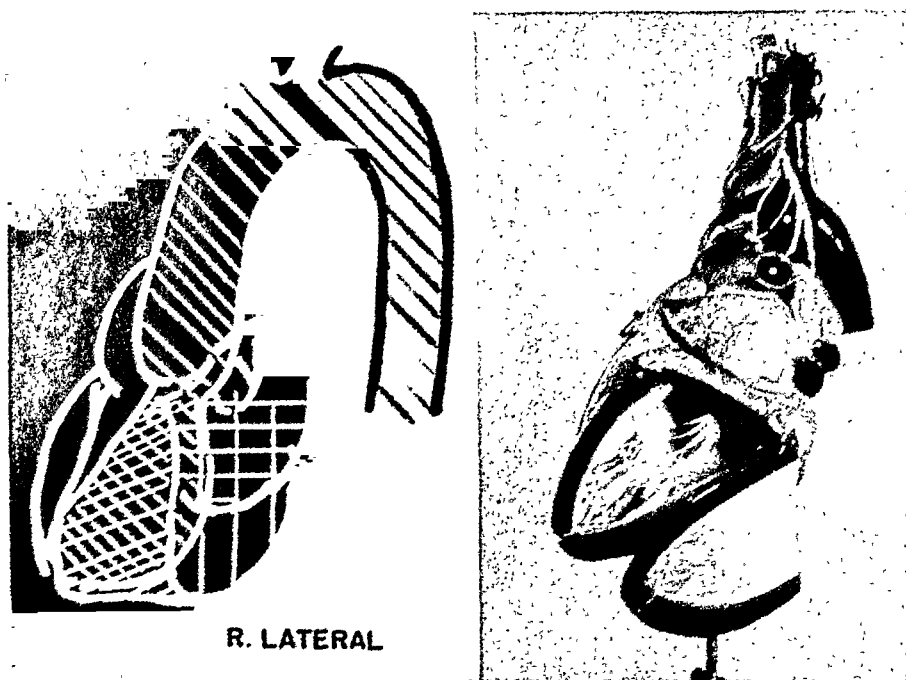
R. LATERAL

Fig. 1B.—Right lateral angiocardiogram. The model is turned into the left lateral position to show the left auricle. (Left ventricle open.)

The dilated right ventricle is hidden within the cardiac shadow in the posteroanterior and left oblique positions, and cannot be defined by any points on the contours. Only in the marked right oblique position does it form part of the contour in the pulmonary conus region. Then, as the patient is rotated into the lateral position, it occupies the entire anterior surface of the heart, obliterating the retrosternal space (Fig. 2). Enlargement of the heart to the right does not appear ordinarily until there is frank right-sided heart failure. It is demonstrable earliest in the left anterior oblique position, and apparently is associated uniformly with dilatation of both the right ventricle and the right auricle.

The same phenomena can be studied in connection with congenital pulmonic stenosis, which, for this purpose, need not be an isolated condition, for a complicating interventricular septal defect does not materially change the findings. In these conditions marked enlargement of the right ventricle is found anatomically. Roentgenologically the heart is enlarged to the left. There is no enlargement to the right,
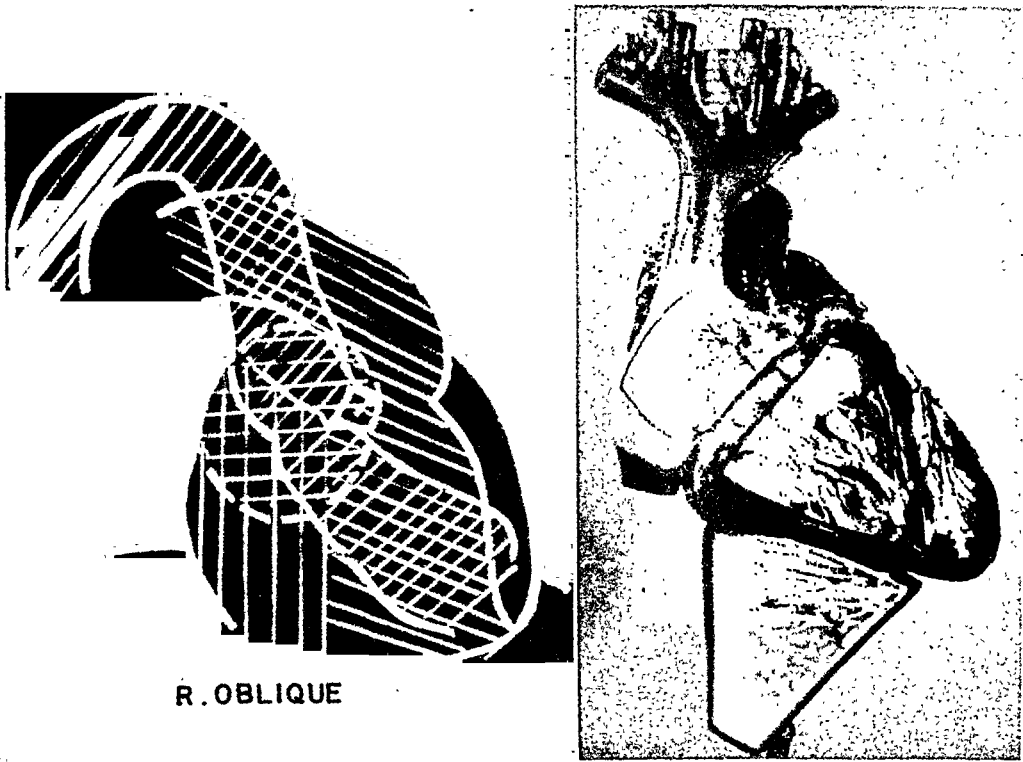
R. OBLIQUE

Fig. 1C.—Right anterior oblique position. (Right ventricle open.)
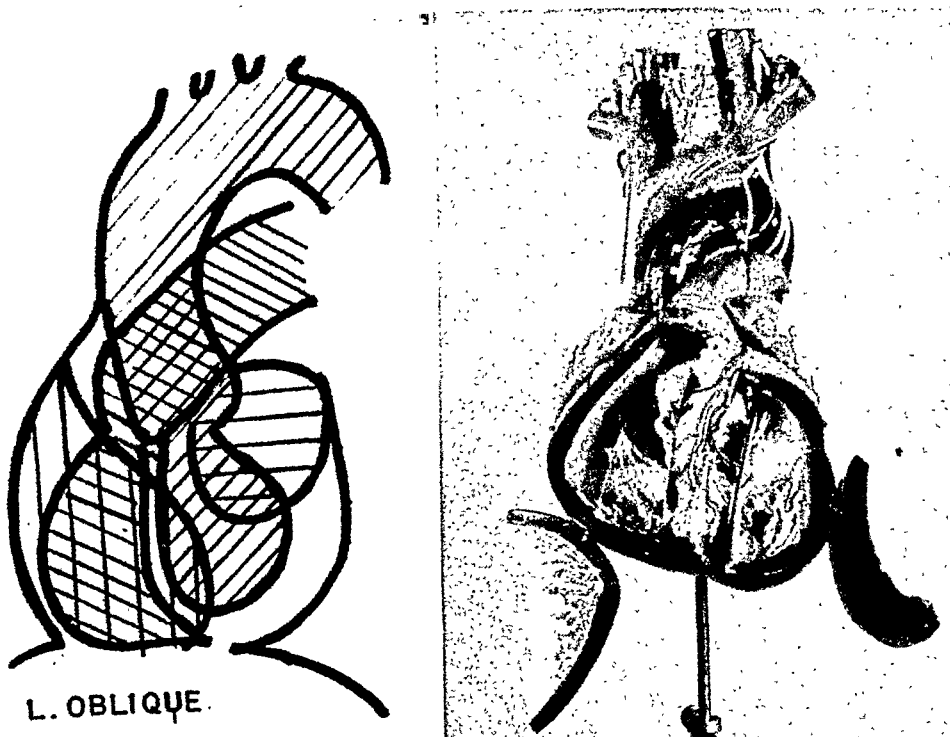
L. OBLIQUE

Fig. 1D.—Left anterior oblique position. (Both ventricles open.)
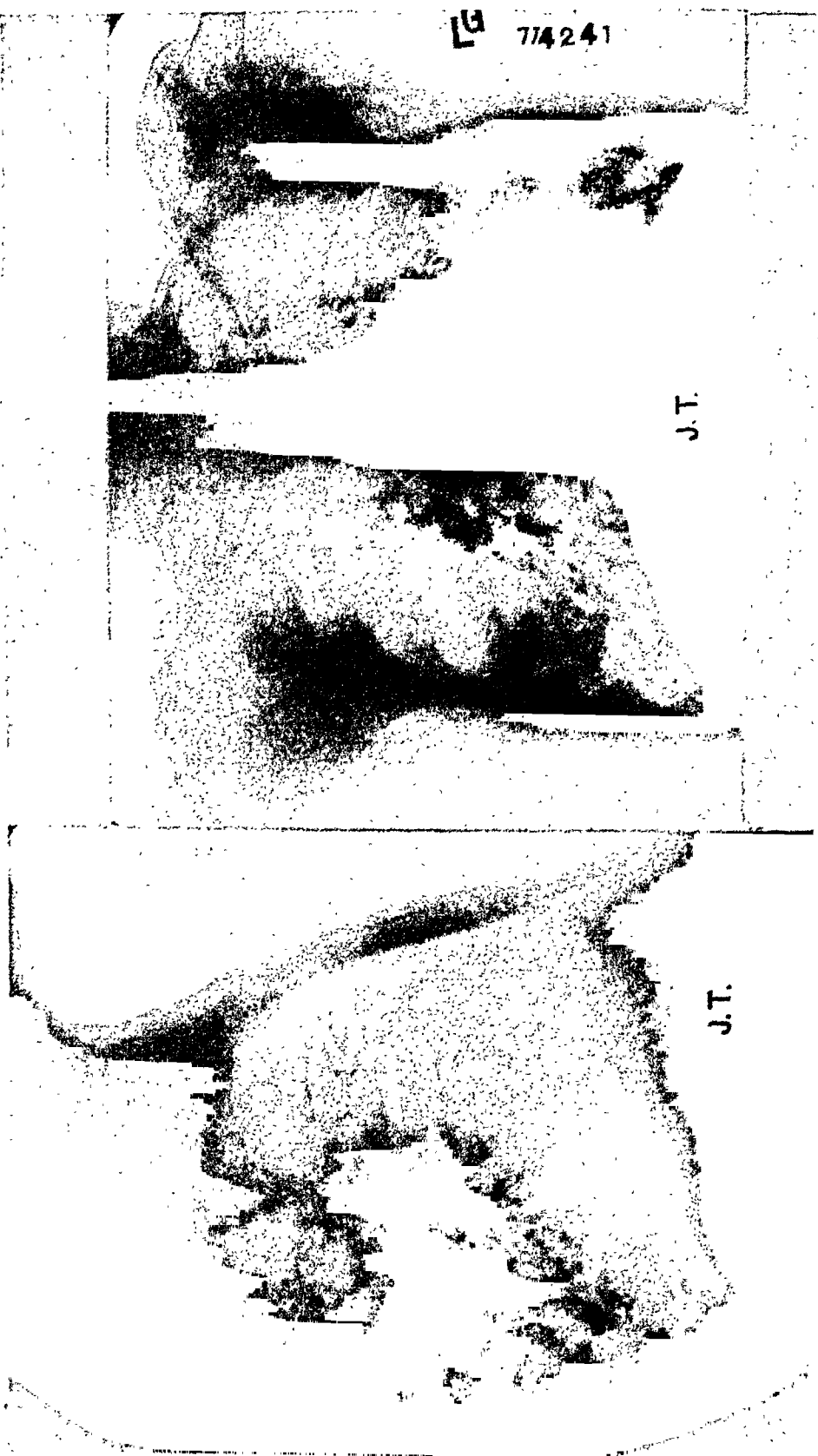
Fig. 2.—Posteroanterior and left lateral views in a case of cor pulmonale as the result of long-standing bronchiectasis. Right-sided heart failure was present for five years. Angiocardiograms and post-mortem examination revealed marked hypertrophy and dilatation of the right ventricle.
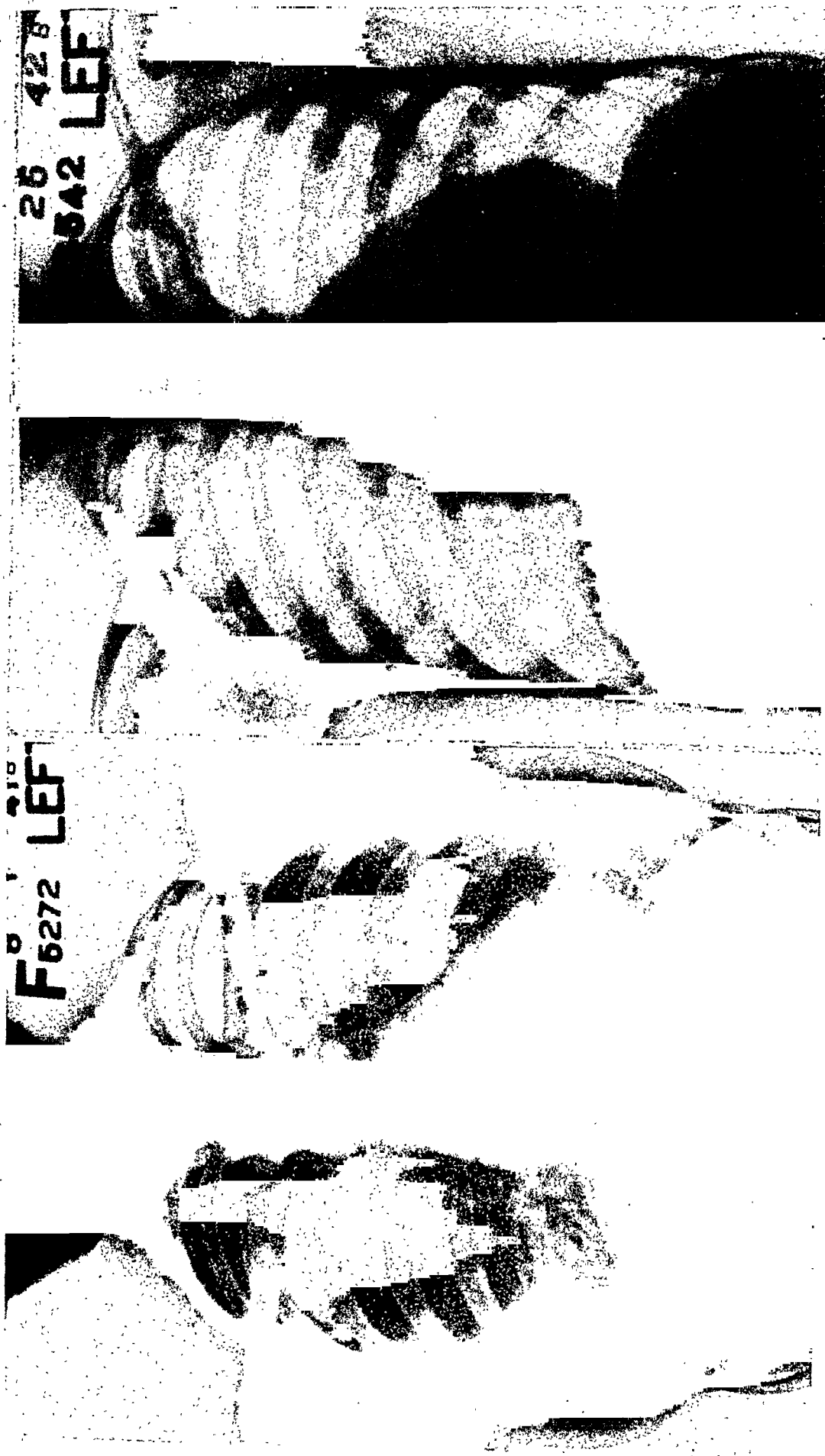
Fig. 3.—Cases of isolated pulmonic stenosis. On the left, the pulmonary artery is small. On the right, there is a poststenotic dilatation of the pulmonary artery. The convex "middle left curve" is due mainly to dilatation of this vessel.

either in the posteroanterior or in the left oblique positions. When the right, ventricular enlargement is mainly hypertrophy, as in the tetralogy of Fallot, the base of the heart just below the level of the pulmonary artery may not be significantly widened. If, however, there is also dilatation, as in isolated pulmonic stenosis, the base of the heart is widened. When, in addition, there is a poststenotic dilatation of the pulmonary artery, the middle left segment becomes very prominent, and the configuration cannot be differentiated roentgenologically from that of cor pulmonale as it is seen in emphysema or pulmonary fibrosis (Fig. 3).
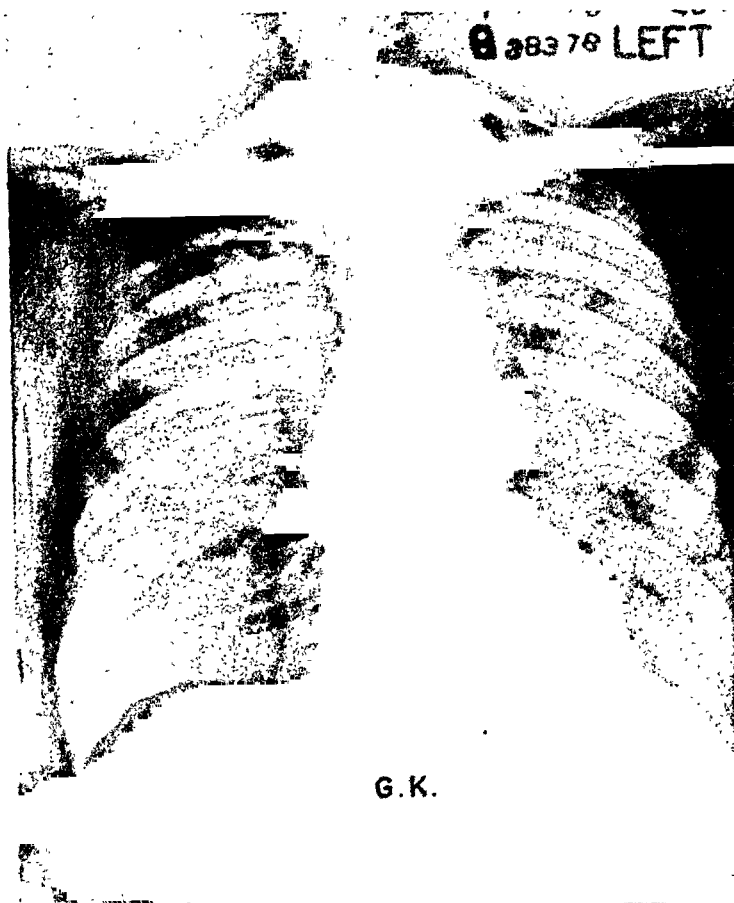
Fig. 4.—Cor pulmonale secondary to pulmonary fibrosis. Post-mortem examination revealed marked enlargement of the right ventricle. The left cardiac chambers were only slightly dilated and hypertrophied.

Since the right ventricle does not come into contour in any positions except the right anterior oblique and the right lateral, it follows that milder degrees of enlargement of this chamber will be demonstrated, if at all, only by displacement of adjacent chambers. For this reason, even moderate enlargement may be difficult to demonstrate and to differentiate from enlargement of the left ventricle. Occasionally, in the lateral view, obliteration of the retrosternal space will point to

right ventricular dilatation, in contrast to the large left ventricle, which intrudes into the retrocardiac space. The latter is demonstrated better in the left oblique view. Furthermore, in the posteroanterior view, widening of the heart just below the level of the pulmonary artery also may point to enlargement of the right ventricle. Neither of these criteria, however, is of great value when the dilatation is moderate and when the chest is barrel-shaped and emphysematous. To illustrate this conclusion we cite the fact that, in chronic emphysema, pathologically the right ventricle is found to be dilated in a high proportion of cases. Nevertheless, radiologically the heart often does not appear enlarged. Only when prominence of the pulmonary artery segment is taken as an indication of right ventricular enlargement, as Parkinson and Hoyle[4] suggested, is the incidence of right ventricular change as frequent as the anatomic data would lead one to expect. Fortunately, this criterion is generally valid because, in emphysema, the pulmonary artery is likely to be dilated when the right ventricle is enlarged. In the absence of pulmonary artery dilatation, the only indication of moderate right ventricular dilatation in emphysema is enlargement of the heart to the left, but this evidence is useless unless clinical data exclude dilatation of the left ventricle, and a pulmonary disease is present in which cor pulmonale might be expected (Fig. 4).

LEFT AURICULAR DILATATION

The outstanding example of predominant dilatation of the left auricle occurs in mitral stenosis. Roentgenologically it is characterized by a straightening or convexity of the middle left cardiac contour in the posteroanterior and right oblique positions. The chamber may be visualized as a dense area within the cardiac shadow; sometimes it projects to the right, and overlaps the right auricular contour. The left main bronchus is elevated, but this is seen better in the left oblique position. In the right oblique and right lateral positions the retrocardiac space is encroached upon. The esophagus is displaced posteriorly, as well as to the right, and is compressed. Angiocardiograms show that the pulmonary artery is elongated, elevated, and bowed anteriorly.[5] It is not ordinarily dilated to any marked degree. The right ventricle also is bowed anteriorly. Except when the left auricle is seen directly, the most accurate criterion of its size is the position of the esophagus. This must be observed critically, however. The impression made on the anterior surface of the esophagus by a predominantly enlarged left auricle is ordinarily sharply localized. It begins immediately below the level of the left bronchus and ends well above the diaphragm.

The right ventricle remains only moderately enlarged in mitral disease until advanced failure supervenes. Since the left auricle displaces

the right ventricle anteriorly, the size of the ventricle cannot be ascertained accurately roentgenologically. Occasionally it may be possible to judge the extent to which it contributes to the heart shadow by subtracting the contribution of the left auricle, visualized as a dense shadow, or suggested by the positions of the esophagus and of the left main bronchus. It may be assumed, also, that the larger the left auricle, the more likely it is that the right ventricle is dilated and hypertrophied. Enlargement of the heart to the right and anteriorly, judged from the left oblique position, often results entirely from displacement of the right chambers by a huge left auricle, rather than by enlargement of the right auricle and right ventricle, as is assumed ordinarily. In the same way, the left ventricle may appear large as the result of displacement, although generally this does not happen to the same extent as with the right chambers.

LEFT VENTRICULAR ENLARGEMENT

Left ventricular enlargement may take the form of concentric hypertrophy, with little or no dilatation (usually associated with hypertension), or eccentric hypertrophy with dilatation. The roentgenologic diagnosis of concentric hypertrophy is made with difficulty. Until there is significant increase in the volume of the heart, which does not occur with concentric hypertrophy alone, the roentgenologic diagnosis must be based upon the shape of the left ventricular contour. This becomes rounded as it is seen in the posteroanterior view, or somewhat better in the left anterior oblique position. However, the degree of "rounding" of a curve is difficult to define for practical purposes, and, considered critically, the observation is of limited value. It is fortunate that enlargement due to mild hypertrophy in hypertension is of no great significance clinically in so far as the cardiac status is concerned. A progressive increase in the size of the left ventricle in hypertension is accompanied by widening to the left and increase in length, and generally can be attributed to an associated aortic insufficiency or to coronary insufficiency. When hypertrophy is marked, so that cardiac volume increases, enlargement is easily detectable by correlating the usual measurements with habitus. The ventricle becomes elongated as well as rounded, and the apex cannot be separated from the gastric air bubble in deep inspiration (Fig. 5).

Concentric hypertrophy with dilatation is manifested first by an increase in the size of the ventricle, particularly in its long diameter. The increase in length is accompanied roentgenologically by enlargement to the left and posteriorly. In order to demonstrate this by measurement, it has been suggested that the length of the heart as a whole (L) be compared with the transverse diameter (T). A long diameter, more than 10 per cent longer than the transverse diameter,

is used to indicate enlargement of the left ventricle. Careful measurements by us, however, failed to confirm the value of this observation, which is not surprising when the definition of the long diameter of the heart is considered. The right cardiac-supracardiac junction has no constant relationship whatsoever to the position of the aortic valve; the latter is deep in the shadow of the heart, and its location is unpredictable unless it is calcified. Hence, the long diameter is not a measurement of the length of the left ventricle. Furthermore, a complicating feature is the fact that the long diameter is not mathematically independent of the transverse diameter. Therefore, until

Fig. 5.—Marked hypertension in a case of coarctation of the aorta. The patient was asymptomatic.

the increased volume is detectable by measurement of the area of the whole heart, it is necessary to rely upon visual impression to ascertain whether the shape of the left ventricular contour is abnormal and whether it intrudes into the gastric air bubble excessively. Further left ventricular enlargement is manifested by widening to the left and posteriorly.

DISCUSSION

In view of the above data, it is well to reconsider what information is made available by cardiac roentgenology. The examination should provide fairly accurate answers to the following questions:

1. Is the heart enlarged? If so, is the enlargement mainly to the left, or is the right side also widened? Is it enlarged at the base just below the level of the pulmonary artery?

2. Is the shape of the heart abnormal when the patient is turned through various positions?

3. Is the left auricle enlarged?

4. Is the pulmonary artery dilated?

5. Are pulsations abnormal in any segments? (Discussion will be limited to myocardial infarction.) ·

From these data alone certain conclusions can be drawn. Predominant enlargement of the left auricle ordinarily indicates the presence of a mitral lesion, which may or may not be associated with other abnormalities. There are very few exceptions. For example, the chamber may be enlarged when the ductus arteriosus is patent and there is no mitral disease.[6] On the other hand, when it is enlarged in conjunction with an atrial septal defect, the mitral valve also is likely to be deformed. It is important to recognize certain variations in the position of the esophagus which simulate pressure by the left auricle alone. For example, the generally dilated heart will displace the esophagus posteriorly as a whole. In an occasional normal person there may be a gentle posterior bowing. In older persons the esophagus may be adherent to the descending aorta and therefore be displaced posteriorly; however, in this event, in the left oblique position it is seen to be separate from the heart and adjacent to the aorta. These conditions may be differentiated from the predominantly enlarged left auricle by the sharply localized pressure of the latter. On the other hand, it must be emphasized that lack of demonstrable enlargement does not exclude mitral disease. There may be no demonstrable left auricular enlargement with an early or functionally insignificant lesion.

The conditions without left auricular enlargement may be discussed in connection with whether or not pulmonary artery dilatation is present. Ordinarily, when the pulmonary artery is dilated the right ventricle also is enlarged. Exceptions are few. In cases of patency of the ductus arteriosus, in 50 per cent of which there is dilatation of the artery, it is the left ventricle, rather than the right, which is enlarged.[7] With idiopathic pulmonary artery dilatation there may be no significant chamber enlargement.[8] The prominent pulmonary artery segment which is seen in some normal adolescents and in Graves' disease may present a roentgenologic problem because it might be thought to indicate a mitral or a congenital lesion. As far as mitral disease is concerned, a predominant pulmonary artery segment is due

to left auricular enlargement, which is, therefore, the more important consideration. Differentiation from a congenital lesion is a clinical rather than a roentgenologic problem.

As far as left ventricular enlargement is concerned, in general, when the heart muscle is not impaired and when dilatation is due to an increase in the stroke output, the ventricle is lengthened in proportion to its width. This abnormality often represents a physiologic reaction, and is reversible when the increased stroke output returns to normal. On the other hand, myocardial damage with left ventricular dilatation is associated with widening of the cardiac shadow to the left and a transverse position of the axis of the heart. Indeed, in the absence

Fig. 6.—Left ventricular aneurysm due to coronary occlusion, associated with a huge left ventricle. The patient suffers only mild dyspnea and fatigue. Aside from two attacks of fresh coronary occlusion, there has been no change in the symptoms during the past fifteen years.

of aortic insufficiency this configuration usually can be attributed to myocardial disease. (The vitamin, mineral, and endocrine deficiencies are excluded from discussion.) It may be said, in general, that, in the clinical evaluation of a patient, it is extremely important to know the size and shape of the left ventricle, and the roentgenologic examination gives these data accurately. Percussion and palpation are not trustworthy. On the other hand, when the size of the left ventricle

is established, differential diagnosis is not aided greatly nor is any information made available in the individual case, from the roentgenologic observation alone, as to the functional capacity of the heart or prognosis (Fig. 6). This statement is not intended to minimize the importance of knowing the size of the left ventricle when it is considered in the light of the clinical diagnosis and other clinical data.

Fluoroscopic examination and, more accurately, the roentgenkymogram give information regarding the condition of the left ventricular muscle by observation of pulsation. There is no doubt that ordinarily this information is obtained more quickly and accurately from the clinical examination and the electrocardiogram. Occasionally, however, when these data are equivocal, an abnormal pulsation will be the only objective evidence of muscle damage, and, at least from the medicolegal point of view, may be very important when found. On the other hand, roentgenkymograms give no indication of functional capacity or of the possibility of future cardiac insults."

CONCLUSION

It is generally realized at the present time that roentgenologic examination of an organ in most instances is only *part* of the clinical examination. This is true particularly of roentgenologic examination of the heart. The current criteria for the roentgenologic diagnosis of heart disease are based often upon physiologic reconstructions which do not occur as simply in practice. Certain important modifications have been suggested as the result of angiocardiographic study. There is no reason to use a method beyond its proper limits to extract information which is of questionable accuracy and which can be obtained more easily by other means. Hence, it is when the roentgenologic observations are considered critically as part of other clinical data that the examination is of real value. Alone, it may be insignificant or even misleading.

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OBSERVATIONS ON THE MECHANISM OF THE PHYSIOLOGIC THIRD HEART SOUND

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ALTHOUGH studies on the physiologic third heart sound have been carried on for many years, there has been no unanimity of opinion as to its cause. In 1907, Gibson[1] came upon the third heart sound in young athletes and in persons convalescing from infectious disease. He recognized the sound on auscultation after his attention had been drawn to it by waves interposed between the v and a waves in the jugular pulse. Gibson considered that the third heart sound may be caused by the floating shut of the auriculoventricular valves during rapid ventricular filling in early diastole. Almost at the same time, Hirschfelder[2] observed h waves in the venous pulse; he suggested that these waves might arise from the momentary diastolic shutting of the cuspid valves, which, in turn, might produce a third heart sound. However, he cautioned that there was no proof for this suggestion. Two years later, Thayer[3] concluded that the third heart sound was valvular in origin. Einthoven[4] studied the problem with a phonocardiograph. He considered the most likely cause of the third sound to be stretching and snapping of the closed semilunar valve membranes in early diastole.

In recent years, other observers have postulated that the third heart sound may be muscular in origin.[5-8] The suggestion was made that, in early diastole, the rapidly distending myocardium becomes suddenly taut, producing audible vibrations. Leonhardt[8] observed regular, sharp, outward movements of the ventricular wall of the dog heart which coincided with a third heart sound. Lewis and Dock,[9] however, studying the origin of heart sounds, concluded that any sound arising from the heart must be valvular in origin because the ventricular myocardium is too thick to permit sudden motions to produce audible vibrations. Recently, Boyer, Eckstein, and Wiggers[10] suggested that the third sound might arise from the impact of the heart against the chest wall. This idea was subsequently investigated by Boyer,[11] who was able to record the third heart sound from the exposed, beating dog heart; he felt that the sound arose from the cardiac wall.

In order to study further the mechanism of the physiologic third heart sound, the following experiments were performed.

METHODS

Dogs were anesthetized with veterinary nembutal. In each experiment the thorax was opened to expose the heart, and an ordinary Starling heart-lung preparation was set up. The heart-lung preparation was used so that a slower ventricular rate and optimum blood pressure and cardiac output could be maintained for the production of clearly recognizable heart sounds.

The heart sounds were recorded directly from the left ventricular myocardium by means of a Wiggers-Dean capsule.[12] The capsule was connected by flexible rubber tubing, about 70 cm. long, to a small glass funnel (2 cm. in diameter) which was placed on the left ventricle immediately above the apex. The capsule membrane was prepared in the usual way;[12] a small mirror (1 mm. square) was applied to the membrane at one edge. Because of the intensity of the heart sounds when they are recorded directly from the heart, it was necessary to render the system less sensitive by placing the mirror as close to the edge of the capsule as possible. The membranes showed a natural frequency of 75 to 85 cycles per second, and were adequately sensitive for our purpose. A suitable optical system was utilized to reflect a light beam from the capsule mirror into an electrocardiographic photokymograph.

The recorded heart sounds were synchronized with electrocardiographic tracings in order to record the events of the cardiac cycle when the heart was beating empty. This was accomplished by embedding one electrode in the right shoulder muscles; the other electrode was inserted into the muscle of the diaphragm in the midline. The heart sounds and electrocardiograms were recorded on the same bromide paper strip.

It seemed desirable to eliminate the possibility that motion of the auriculoventricular valves may produce the third heart sound. Valve motion was prevented by means of special valve "splints." The "splints" were small discs, 1 cm. in diameter, to which rods were attached perpendicularly at the centers. The discs were then passed through small incisions in the right and left auricular appendages and were pushed into the ventricular cavities. When in place, the splints were so small that ventricular function was not hindered; with the heart beating empty, traction could be applied to the rods to hold the valves in a position of closure and to prevent any motion of the membranes. After each experiment the heart was incised and the position of the splints was verified.

During each manipulation of the experiments, careful auscultation was carried out on each heart in order to confirm sound elements noted in the curves.

RESULTS

The Third Heart Sound in the Normally Beating Heart.—When the bell of a stethoscope was placed on the left ventricle above the apex, a third heart sound was invariably heard in early diastole. This sound was distinct from the second heart sound. It seemed short and dull, with a quality of sound like a short *puff* or *pud*, and was less intense than either the first or second heart sounds. Sudden distention of the ventricles occurred simultaneously with the third sound, as nearly as one could judge by concomitant auscultation and inspection of the heart.
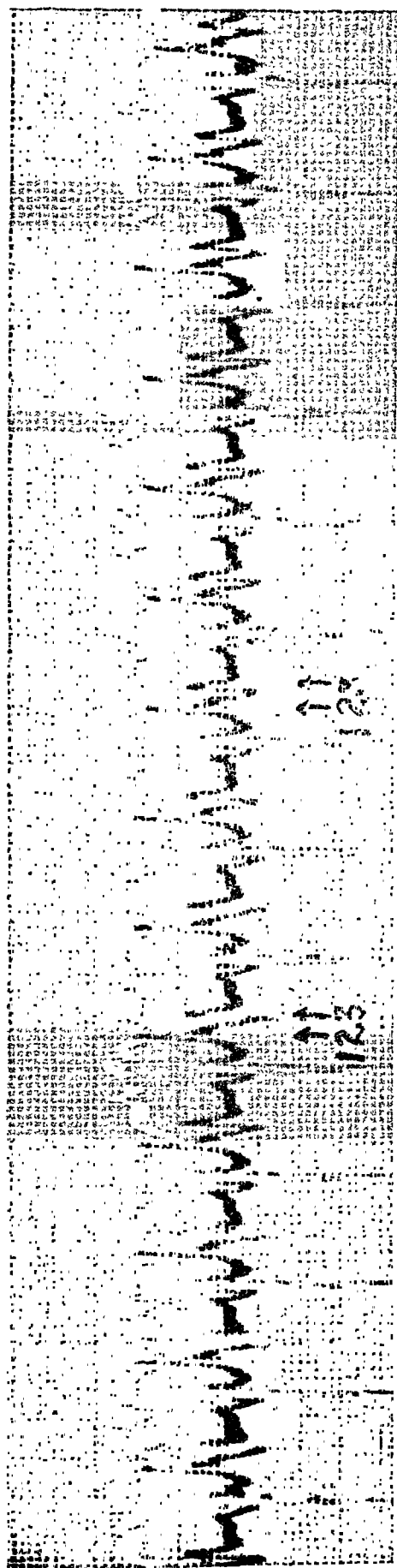
Fig. 1.—Heart sound tracing and electrocardiogram simultaneously recorded from the normally beating heart (heart-lung preparation). Sounds were recorded from the left ventricle just superior to the apex. The three heart sound deflections are clearly recognizable (marked 1, 2, and 3). In this instance the third heart sound is represented by a diphasic, peaked deflection, occurring after the apex of the T wave.

Records of the heart sounds (also taken from the left ventricle just superior to the apex) showed the first sound as a group of large, peaked deflections followed by the finer deflections of the second sound (marked as *1* and *2* in Fig. 1). The first sound waves accompany and immediately follow the R wave of the electrocardiogram; the second sound occurs at the peak of, or on the descending limb of, the T wave. The deflection representing the third heart sound follows the second sound by approximately 0.08 to 0.15 second. In the records it usually appeared as a simple, peaked wave, inverted or upright, often preceded and followed by smaller spikes in opposite direction to the higher point. Occasionally the third sound wave was diphasic in contour. The amplitude of the wave was generally somewhat less than that of the second heart sound.

Considering all of these factors, it seemed probable that the deflection occurring in early diastole represented the physiologic third heart sound.

Effect on the Third Heart Sound of Preventing Venous Inflow and Splinting of the A-V Valves.—Studies with the valves immobilized and the heart beating empty were carried out on seven preparations. Continuous tracings were made throughout the procedure. When control records (and auscultation) had been made with the valve splints in the ventricular cavities and with the heart beating normally, the venous inflow into the heart was shut off. Tension was applied to the splints when the cardiac output had become nil. On auscultation, within a few beats after stopping the venous inflow, there was an abrupt diminution, then complete absence, of the second heart sound. The first sound remained clear, but seemed shorter and more dull. The third heart sound remained distinctly audible, although less intense; it persisted, along with the first sound, as long as myocardial contraction remained vigorous. With re-establishment of venous inflow and release of the cuspid valves; the second heart sound returned as blood pressure was restored; the first and third heart sounds became sharper and more intense.

Fig. 2 shows a continuous tracing of one of these experiments. In the control tracing (*A*) the first and second heart sound deflections are readily identified by their sharp, peaked profiles and by correlation with the electrocardiogram. The third heart sound is represented by a steeply inverted, pointed wave, following the second sound by about 0.1 second, and occurring just after the T wave. When venous inflow was stopped and the A-V valves splinted, the second heart sound was lost within a few beats (*B*). However, the third heart sound persisted, becoming shallower and less sharp (although audible). The finer serrations of the first heart sound disappeared, leaving the coarser waves. With the restoration of venous inflow and cessation of tension on the A-V valves, myocardial efficiency was quickly restored (*C* and *D*); the second heart sound waves returned, the third sound waves became deeper, and the entire curve resumed its "normal" shape.
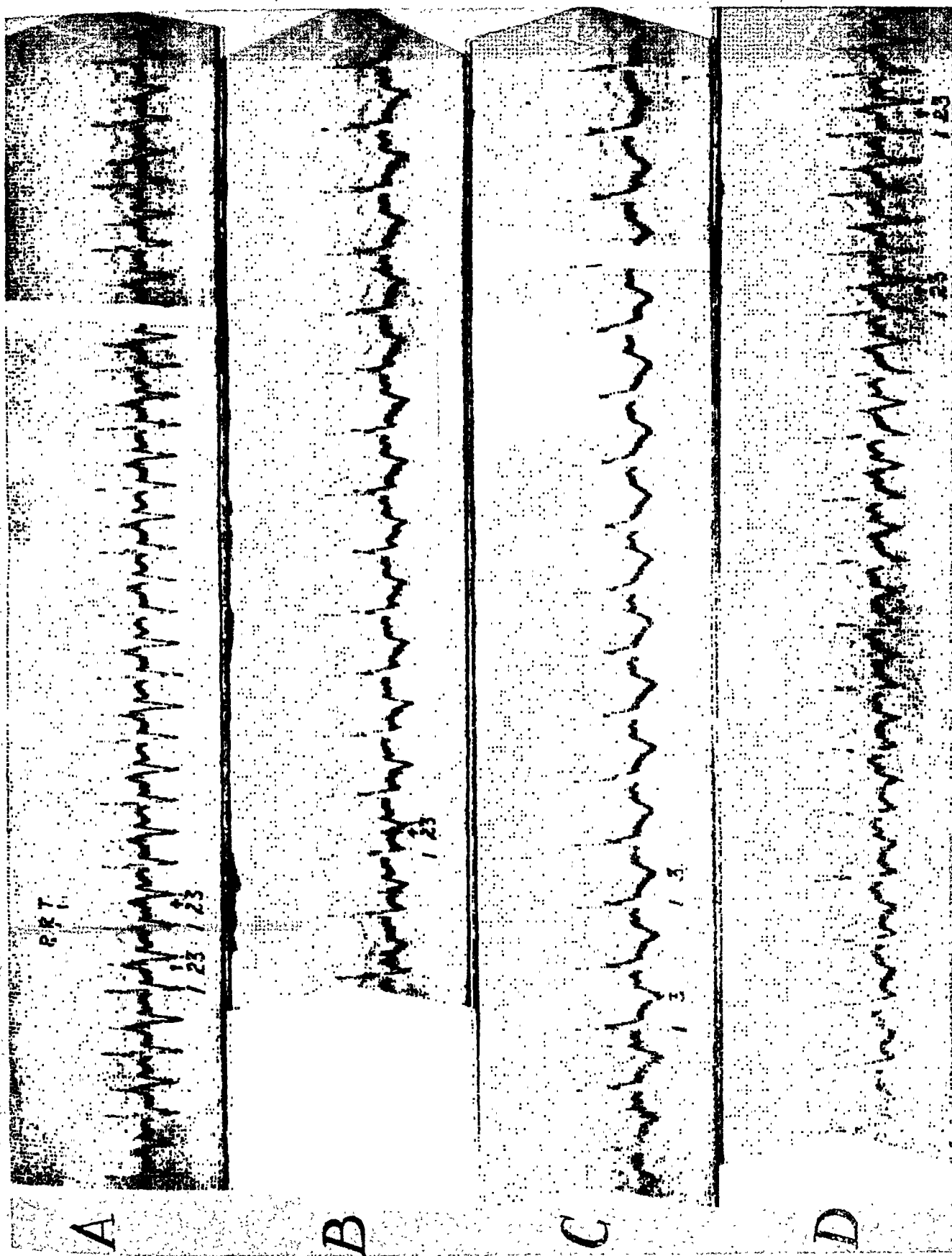
Fig. 2.—Continuous tracing of heart sounds and electrocardiogram during whole of an experiment. Curve A, of the normally beating heart, shows the three heart sounds clearly (marked). The vertical white mark in A is the point where venous inflow was cut off and "splints" placed on the A–V valves. In curve B, the second heart sound has gradually disappeared with the heart beating empty; the first and third heart sounds persist (curves B and C). Vertical white mark in C is point where venous inflow was re-established and the A–V valves released. Curve D shows gradual return of cardiac function; note reappearance and increasing amplitude of second heart sound. Changes noted in the heart sound tracing were confirmed by auscultation of the heart.

The Third Heart Sound in the Empty, Beating Heart Without Valve Immobilization.—In seven heart-lung preparations, venous inflow was stopped without splinting of the cuspid valves. In each experiment the first and third heart sound waves were found to persist while the heart was beating empty; the second sound disappeared with loss of blood pressure. The recorded tracings did not differ materially from those obtained from the empty beating heart with the valves immobilized. As with the former experiment, the first and third heart sounds could be heard during the period when there was no inflow into the heart.

DISCUSSION

The accurate identification of any "sound" arising from the heart will depend on (1) audibility, and (2) the graphic recording of the "sound" so that it may be studied with respect to other heart sounds and to the cardiac cycle. These conditions appear to have been fulfilled with regard to an early diastolic heart sound in the exposed, beating dog heart.

The third heart sound, on the tracings, always appeared in simpler contour than the first or second heart sound deflections (Fig. 1). Generally, a dominant upright or inverted, pointed wave occurred, often preceded and followed by smaller peaked deflections in opposite phase. When the heart beat empty, the third sound waves became of less amplitude (although retaining a pointed contour), and the smaller opposing waves were lost (Fig. 2). More important is the fact that a sound, in early diastole, was *audible* as long as the strength of myocardial contraction was maintained.

The persistence of the diastolic sound with the heart beating empty and with arrest of motion of the auriculoventricular valves introduces the possibility that the sound arises from the heart wall. Experimental evidence suggests that sounds from myocardial contraction may be recorded as simple waves with steep, sharply defined onsets. Smith, Gilson, and Kountz[12] studied the muscular element of the first heart sound by introducing balloons into the ventricular cavities and inflating the balloons to restrain all motion of the auriculoventricular valves. The sounds were recorded with a cathode-ray oscillograph. They found that a short, dull sound could be heard at the onset of systole, corresponding to the time of the first heart sound when the valves were thus immobilized. They further observed that a sharp, single decrement occurred in the oscillographic tracing synchronous with the sound. These observers postulated that the myocardial muscle fibers may represent, in a sense, a vast number of lax cables; when the muscle contracts, the lax fibers become suddenly taut in toto, producing audible vibrations.

Gilson[14] has recently observed the sharpness and dullness of clicks developed from simple electrical wave forms. He used a triode amplifying tube, so arranged that a telephone receiver was activated by the

plate current; upon opening a switch in the grid circuit, the plate current increased along a somewhat S-shaped time course; the rise at the foot of the curve was much more abrupt than was the approach to plateau level. The conclusion was reached that the click produced by the current change was represented by the upswing early in the curve. The sound was a click which had a sharper or duller quality according to whether the onset of electrical change was more sudden or more gradual. From these observations, it seems quite probable that the dull or sharp quality of a heart sound, such as the third sound as recorded in these experiments, may be due to relatively simple impact phenomena; other vibrations may be superimposed on these to modify the general quality of the heart sound. It also offers clarity to the fact that the rather simple wave forms which occur at the onset of systole and in early diastole, with valvular elements eliminated, have definite acoustic properties.

With this experimental evidence at hand, it appears that the third heart sound, at least in part, arises from the heart wall. Furthermore, since the third sound occurs at the time of rapid ventricular filling, it is possible that abrupt stretching of the myocardium produces the sound, as was suggested by earlier investigators.[5-8]

Boyer[11] was able to record third sounds directly from the myocardium by using a small, shallow bell placed on the heart. In addition, he found that a sound, identical with the third heart sound, occurred when the heart was allowed to strike the receiving bell gently. The force necessary to produce this sound was extremely small. Since third heart sounds were also noted when the heart was placed in a glass cardiometer, where no impacts were possible, he concluded that the phenomenon arose from the heart wall. Our conclusions are in essential agreement with his. On the other hand, Dock[15] and Lewis and Dock[9] have contended that the myocardium is so thick that its movements do not produce sounds. They state that motion of the valves is the only possible source of sound from the heart. Although valvular elements contribute largely to the first sound, and probably entirely to the second sound,[13] this does not appear to be true of the early diastolic third heart sound recorded from the dog heart. Dock's contention, therefore, is not supported by the observations of Boyer[11] nor by the experiments reported here. Indeed, it seems definite that any motion of the heart, whether valvular or muscular, may produce a sound, provided the motion is of sufficient strength and abruptness of onset.

These experiments emphasize again the presence of elements initiated by the heart wall in the first heart sound. The *first*, as well as the third, sound was noted in the procedures involving restraint of the cuspid valve leaflets, and the resulting first sound wave became nearly as simple as the deflection of the third heart sound.

SUMMARY

An early diastolic third heart sound was heard on direct auscultation of the left ventricle of the heart-lung preparation. Tracings of the heart sounds, using a Wiggers-Dean capsule, showed a deflection early in diastole which was apparently synchronous with the sound.

When blood flow into the heart was cut off, so that the heart beat empty, and motion of the cuspid valves was eliminated by splinting of the leaflets, the first and third sounds persisted.

It was concluded, therefore, that the third heart sound, as recorded from the normally beating dog heart, may arise from the heart wall. The observations further indicated that a mechanical disturbance of apparently simple wave form may have acoustic value, and that the third heart sound is often of this form.

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Clinical Reports

CLINICAL ARREST OF ENDOCARDITIS LENTA BY PENICILLIN

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FLOREY and Florey[1] reported the use of penicillin in the treatment of one patient (Case 15) with endocarditis due to *Streptococcus viridans*. The penicillin was administered at intervals of one to three hours for thirty days (total dose, 4,670,000 units). During this time there was marked improvement. After the penicillin was discontinued, the temperature mounted to its original height in a week, appetite was lost, and the blood culture again became positive at the end of three weeks. The patient died after another three weeks. The streptococcus apparently developed a considerable resistance to the penicillin.

Keefer and his committee[2] reported disappointing results in the treatment of endocarditis with penicillin. Loewe and his associates,[3] on the other hand, have reported a series of unbroken successes in the treatment of bacterial endocarditis with penicillin and heparin, and, more recently,[4] have reported observations on a larger number of patients with only a few failures.

During many years of continued study of endocarditis, we have observed very few survivals. In our series there have been two examples of recovery from clinically evident staphylococcic endocarditis and three recoveries from meningococcic endocarditis; all five patients were well at the last report, two to six years after apparent cure. In all five the diagnosis was based on clinical signs and persistently positive blood cultures. Until 1943, we had not observed a single instance of genuine arrest of endocarditis due to *Streptococcus salivarius*, which is evidently the commonest form of so-called subacute bacterial endocarditis. At present we have under observation several patients in this category in whom the course of the disease has been favorably influenced by the use of penicillin. A detailed report of one example of apparent arrest of the disease would seem to be of scientific as well as of general human interest, particularly because the successful treatment in this case followed a long period of deterioration which was thought to have attained the terminal stage.

CASE REPORT

M. F.. aged 32 years, a graduate nurse and the wife of a physician, previously healthy and without signs of cardiac defect, had an inflamed tooth extracted, in the usual sitting position, on Feb. 22, 1943. After this there was a persistent fever; this was at first ascribed to osteomyelitis of the jaw, but, after the development of a mitral murmur and the recovery of bacteria from the blood, it was recognized as the fever of bacterial endocarditis. The patient was admitted to the New York Post-Graduate Hospital on April 30, 1943, with the diagnosis already established. The most important subsequent observations are indicated on the graphic charts.

The period from April 30 to May 31 shows the sort of record that is commonly observed when a sulfonamide is administered. The systolic murmur, the positive blood culture on April 30, the petechia in the finger on May 1, and the accelerated erythrocyte sedimentation rate on May 3, along with elevated temperature and pulse rate, present a characteristic picture. Sulfadiazine, in a dose of 6 Gm. per day, with strict rest in bed, brought about some amelioration, but the bacteria persisted in the blood stream (12 per milliliter on May 17, and 18 per milliliter on May 24). The abnormal sedimentation rate remained evident and a new embolic spot appeared on May 16. On May 17 the administration of thiobismol, in a dose of 15 mg. twice daily by intravenous injection, was initiated. and. on May 19, intravenous injections of small amounts of citrated blood² were begun. The detail of these treatments may be followed in the charts.

In the next thirty-two days, from June 1 to July 2, there was more evidence of deterioration. Embolism to the brain on June 1 and the development of dysuria on June 6 caused us to discontinue the sulfadiazine. An antivirus filtrate, prepared by filtering an old autolyzed. culture of the specific streptococcus, was given by daily intravenous injection from June 5. Neoarsphenamine in small doses was substituted for the thiobismol from June 9 to 12. The temperature attained a higher level: many conjunctival petechiae appeared; there was blurred vision and, on June 14. a hemorrhagic spot appeared in the right ocular fundus; the blood pressure fell. and emaciation rapidly progressed. The blood culture of June 14 developed 90 colonies per milliliter of blood. Chills and vomiting added to the distress of the patient. She received the last rites of the Church on June 18. In desperation, the sulfadiazine was started again on June 22, but was quickly discontinued. A limited quantity of partially processed penicillin became available on June 23. and this was found to exert a very powerful bacteriostatic effect in vitro upon the streptococcus of this patient. It was therefore administered by intramuscular injection in small doses, estimated as 100 to 200 Oxford units. every three hours. The supply of blood for transfusion failed on June 28, and intravenous injections of an iron preparation were given. On July 1 bilateral retinal emboli occurred, resulting in serious impairment of vision.

In the thirty-two days from July 3 to August 3 there were progressive loss of weight. mental confusion, a definite cerebral insult on July 21, splenic infarction on July 31. and slight hematuria on August 3. The available penicillin was sufficient for only small doses. The daily small transfusions doubtless helped to prolong life. The temperature tended to a lower level after July 25, and one gained the impression

that the slightly larger doses of penicillin might be contributing something of value.

From August 4 to 15 there was distinct improvement, and every effort was made to obtain increased supplies of penicillin for the patient, but without success. It was necessary to reduce the dose to approximately 100 units every three hours on August 15. The temperature rose and a

Fig. 1.

Fig. 2.

Fig. 3.

severe infarction of the spleen on August 17 caused us to omit the transfusions for a time. By the last of August the end seemed near. Inability to take or to retain food, physical exhaustion, and emaciation were extreme. At this time, however, we received word of encouragement in regard to supplies of penicillin, but the immediate change in the situation resulted in complete lack of this drug from September 4 to 9.

MF | JUN 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | JUL 1 | 2

105 104 103 102 101 100 99

T

CHILL

LAST RITES

EXHAUSTED

CHILL 25 MINS

CHILL

63 BLOOD CULTURE 43

BLOOD CULTURE 29

BP 98/60

CHILL

CHILLY

PETECHIA R GREAT TOE

CHILLY

CHILL 15 MINS

SULFADIAZ-INE GRAMS)1

BP 90/54

CONJUNCTIVAL EXTRAVASATIONS

BLURRED VISION

EMBOLISM RETINAL BILATERAL

150 130 120 110 100

P

41 SED RATE

DEPRESSED

SED RATE 75

EMESIS

THIOBISMOL MG IV 10 20 10 10 10 10 10 10

THIO-BISMOL MG IV) 10 10 10 10 10 10 10 10

PENICILLIN DOSES EVERY 3 HOURS — 100 ? — 150 ? — 200 ? — 150 ? 200 ? 100 ? UNIT DOSES

BLOOD ML IV) 50 50 25   25 50 25 25 25 50 50 50 50 25 50 25 50 25 50 25 40 40 40   20   5 ML FRAISSE FE IV 5

ANTIVI-RUS ML) 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4

Fig. 4.

MF | JUL 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18

105 104 103 102 101 100 99

T

NAUSEA CONFUSED

DROWSY

CHILL CHILL

CHILL 30 MINS

BILATERAL HEMORRHAGIC RETINITIS

87 BLOOD CULTURE

BLOOD CULTURE 21

BLOOD PRESSURE 102/54

103/57 BP

DISORIENTED AT TIMES

90/50   B P   98/54

130 120 110 100 90

P

60 SEDIMENTATION RATE

COUGH EMESIS

SED RATE 31

EMESES

CHILLY

THIOBISMOL MG IV 20 20 15 10 15 10 15 10 15 10 15 10 15 10 15 10 15 10 15 10 15 10 15 10

BLOOD ML IV   20 40 40 40 80 80 50 30 40 80 80 80   70   40 80 40 40 40

PENICILLIN EVERY 3 HOURS
DOSES — 100 ? UNITS — 200 ? UNITS — APPROXIMATELY 50 UNITS EVERY 3 HOURS 9 AM JULY 8 THRU JULY 18

ANTIVIRUS ML IV 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4

Fig. 5.

MF | JUL 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | AUG 1 | 2 | 3

103 102 101 100 99

T

SPEECH THICK

SPLEEN LARGE & TENDER

DEPRESSED SLIGHT HEMATURIA

CEREBRAL INSULT

TONGUE PROTRUDED TO THE LEFT

112/84 BP

67 BLOOD CULTURE

43 BLOOD CULTURE

CONJUNCTIVAL HEMORRHAGE

130 120 110 100 90

P

65 SED RATE

RIGHT FACIAL PALSY

98 SED RATE

105 SED RATE

EMESES

CONJUNCTIVAL PETECHIAE

CONJUNCTIVAL PETECHIAE

THIO-BISMOL MG IV) 15 10 15 10 15 10 15 10 15 10 15   15 10 15 10 15 10 15 10 15 10 15   15 10 15 10

BLOOD ML IV) 40 25   40 80 80 80   80 40 80 80 80 120 70 40 80 80 120 60 80 80 80 120 80 40

PENICILLIN DOSES EVERY 8 HOURS
UNITS 100 ? — 150 ? — 200 ?

ANTIVI-RUS ML) 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4 1/4

Fig. 6.

MF	AUG 4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19

BRIGHTER   ALERT STRONGER   VISION IMPROVED

T 103 102 101 100 99

11 BLOOD CULTURE   1 PER ML BLOOD CULTURE   BLD CULT 30   SPLEEN SWOLLEN & TENDER

P 140 130 120 110 100

109 SED RATE   SED RATE 87

THIO-BISMOL MG IV: 15 10 15 10 15 10   15 10 10 10 15 10 15 10 15 10   15 10 15 10 15 10 15 10
BLOOD ML IV: 80 80 80 40 55 40 80 80 80 80 40 35 40 80 80 80 75 80 80 40 80 80   80 40 80 80
PENICILLIN: DOSES 150 ? UNITS   DOSES 200 ? UNITS   DOSES 250 ? UNITS   DOSES 100 ? UNITS
ANTIVIRUS ML: 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4

Fig. 7.

MF	AUG 20	21	22	23	24	25	26	27	28	29	30	31	SEP 1	2	3	4

PAINFUL L SHOULDER   COUGHING   WEEPING   EMACIATED

T 107 103 102 101 100 99

114/78 BP   EXHAUSTED
EMESES ? ?   ? ? ? EMESES
67 COLONIES PER ML IN BLOOD CULTURE 90   NAUSEA
69 SED RATE   SED RATE 95

P 130 120 110 100 90

COUGH   CHILLY   BP 99/58

THIO-BISMOL MG IV: 15 10 15 10 15 10 15 10 15 10 15 10
MAPHARSEN MG IV: 4 4 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6
BLOOD ML IV: 80 80 80 80 80 80 80 80 80 40 80 120 120 105
PENICILLIN DOSES APPROXIMATE UNITS EVERY 3 HOURS
100 ? —150 ? UNITS FROM 9AM AUG 21   150 ? UNITS TO 9 AM SEP 4
ANTIVIRUS ML: 4 4 4 4 3 4 4 4 4 4 4 4 4 4 4 4

Fig. 8.

MF	SEP 5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20

DISTURBED VISION   RESTLESS   MUCH SPUTUM
RESTLESS

T 103 102 101 100 99 98

BP 110/58   COUGH   MANY CONJUNCTIVAL PETECHIAE   IMPROVED VISION   BP 123/80

EMESES ? ? ? ? ? ? ? ? ? ? ? ? EMESES? ?

P 130 120 110 100 90 80

63 SED RATE   33 SED RATE   SED RATE 26
NAUSEA
75 BLOOD CULTURE   148 BLOOD CULTURE 290   BLOOD CULTURE

BLOOD ML IV: 40 120 120 80 80 120 120 60 40 120 120 120 105 40 120 120

SALINE SOLUTION ML IV 200 1000 1000 1000 800 500

THIO-BISMOL MG IV: 15 30 15 15 10 15 10 15 10 15 10 15 10 15 10 15 10 15 24000 UNITS 40000 UNITS 2000 NITS PER HOUR
TOTAL 11000 UNITS   1000 UNITS EVERY HOUR

PENICILLIN { APPROXIMATE UNITS EVERY 3 HOURS
150 ? 200 ?

ANTIVIRUS ML: 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4

Fig. 9.

The period from September 5 to October 6 included the turning point from utter despair to encouraged optimism. The period of total lack of penicillin was terminated on September 9 by the miraculous renewal of the former meager supply, which was, however, inadequate to halt the progress of deterioration. The blood culture on September 6 developed 75 colonies per milliliter of the patient's blood, that taken on September 13 developed 148 colonies, and one taken on September 16 developed 290 colonies per milliliter. However, on September 15, a dramatic release of the supply of penicillin permitted the administration of 11,000 units from an icejacket container by intravenous drip from 2:30 P.M., September 15, to 8:30 A.M. on September 16. This was followed by 44,000 units from noon to midnight. Then there was an interruption due to technical trouble with the drip. This was started again at 10:30 A.M. on September 17, and continued with some irregularity until 4:00 A.M., September 18, when a total of 40,000 units in 1,000 ml. of saline had been given. Again there was an interruption. However, at 8:15 A.M. on September 18, the administration was systematically arranged so that the penicillin could be given every hour by direct intravenous injection during the day and by injection into the rubber tube of the saline infusion during the night without interruption. This program was followed until September 27, with an increase of penicillin to 3,000 units per hour for a short time on September 25, and then 2,500 units per hour to September 27. This technical method would appear to be most economical with respect to the expenditure of penicillin, but it required almost constant attention. Furthermore, the continuous infusion at night was resented by the patient as she became more alert. On September 27, the technique was revised so that the penicillin was given every two hours, by direct intravenous injection when convenient and by intramuscular injection at other times, ordinarily at night. Interruption of sleep at night proved not to be very serious for the patient.
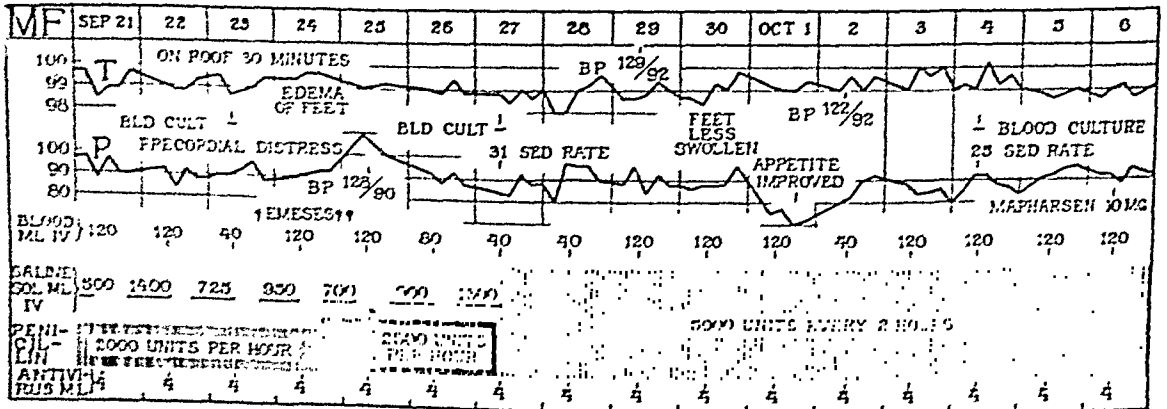
Fig. 10.

The response was very dramatic. The fever declined on September 17, and the blood culture taken on September 20 remained sterile, as did all subsequent blood cultures. There was evidence of pulmonary congestion and possibly pneumonia, with abundant sputum, on September 19 and 20. The blood pressure rose to 123/80 on September 20.

The period from October 7 to November 7 was one of slow convalescence, with gradual increase in weight and return to normal of the sedimentation rate. On October 18, the penicillin program was changed
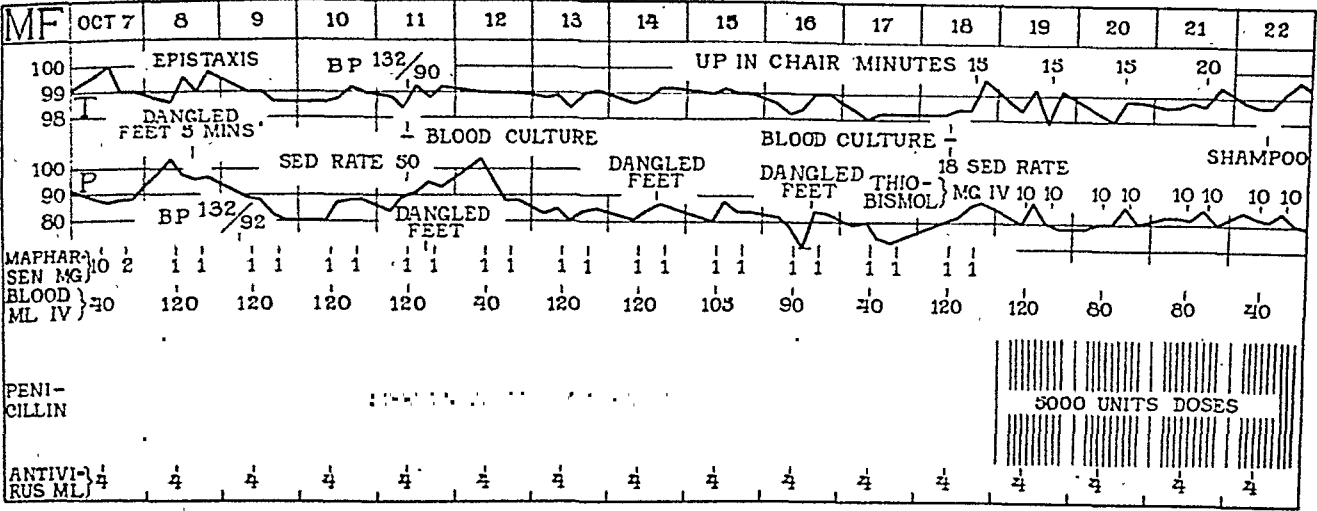
Fig. 11.
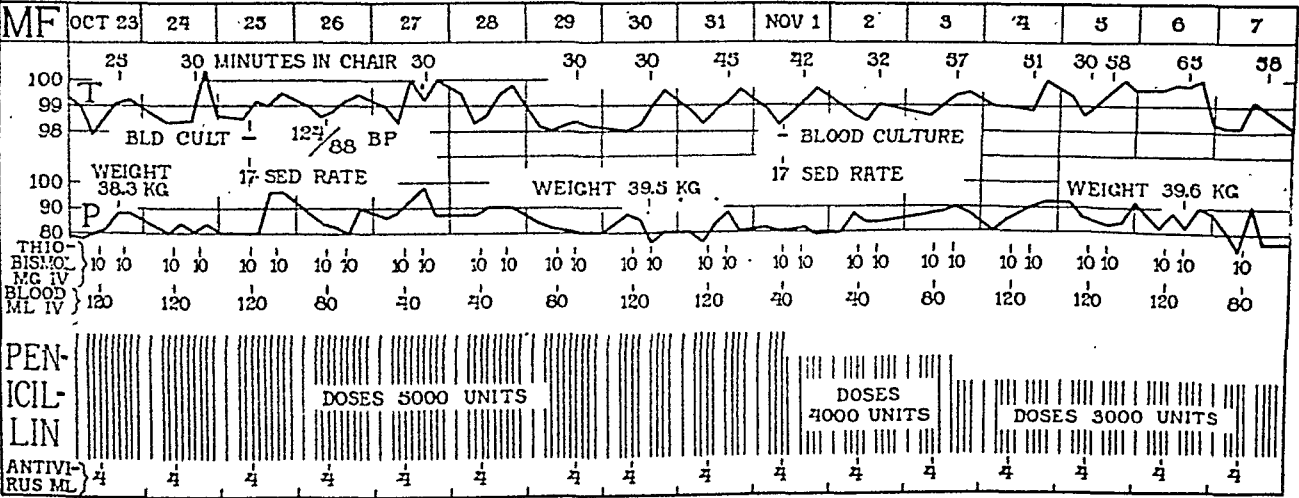
Fig. 12.
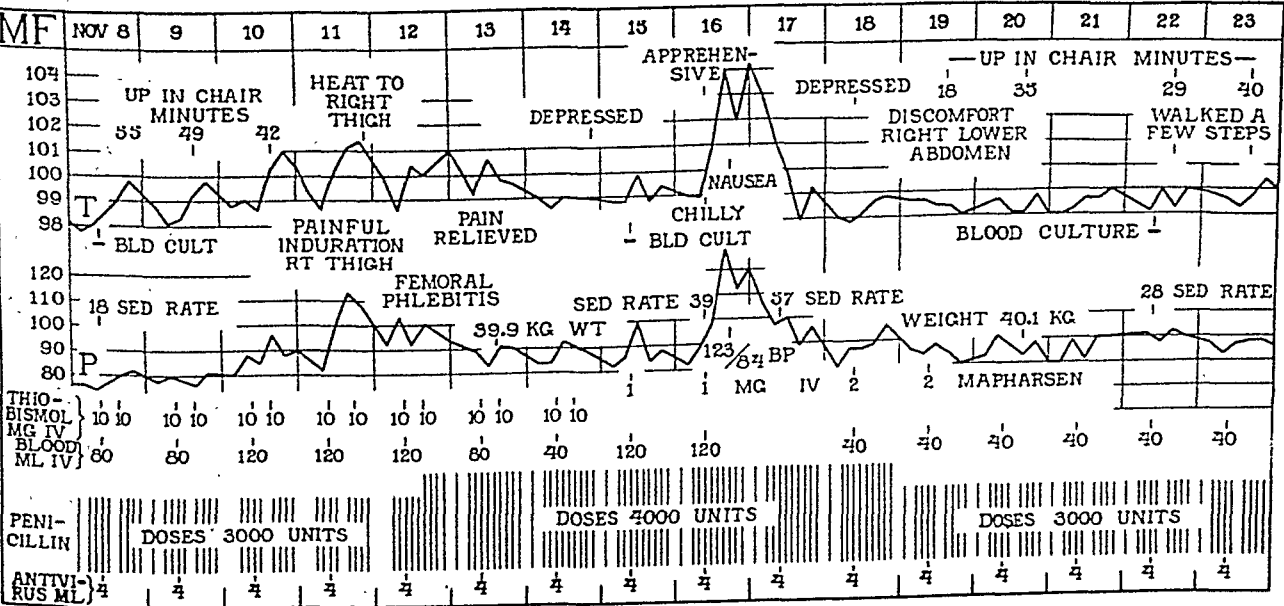
Fig. 13.

to allow intervals of four hours between doses at night, and, on October 30, the dose previously given at 1:30 P.M. was also discontinued. This saved annoyance to the patient and effort of the clinical staff, but was probably not a makeshift to be recommended.

From November 8 to December 9 was a period of uncertainty as to the best procedure. Success seemed assured if only we could continue on the proper course. The patient was eating well and gaining weight and strength, but was still very weak. Apparently she strained her right thigh on November 10 while getting back into bed, and femoral phlebitis was recognized on November 12. Activity was at once restricted and the dosage of penicillin increased. On November 16 there was a sharp rise in temperature, associated with chilly sensations and nausea. Pulmonary embolism was suspected, but this suspicion was not confirmed by physical examination. The sedimentation rate was disturbed at this time; it was 39 mm. per hour on November 16, and 57 mm. per hour on November 18. The spleen, which had been easily palpated for several months, still remained hard and extended 3 cm. below the costal margin on November 19. It was no longer sensitive to palpation. Improvement was quickly re-established, and, after November 26, the patient was up and about daily. There was a remarkable increase in her appetite, and the effect of this was reflected in the increased weight.
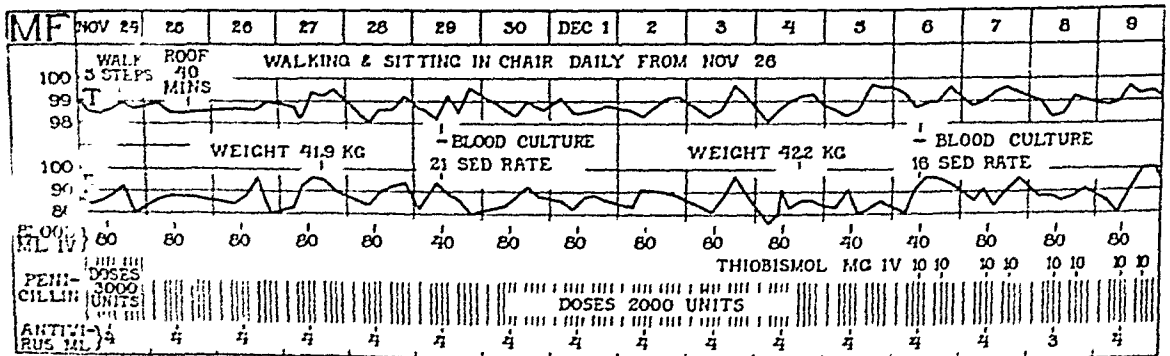
Fig. 14.

In the period from December 10 to January 10 there was first the psychological problem of keeping the patient in the hospital, for as yet she seemed not to have realized the nature of her ailment. It was perhaps fortunate that a toothache developed on December 20, permitting the diversion of dental consultation and roentgenographic study of the entire mouth. It was decided to extract two adjacent offending teeth. After stepping up the dose of penicillin these teeth were removed by Dr. Harold S. Vaughan on December 30. They were devitalized teeth and came away in fragments after considerable trauma to the bone. Profuse and continuous hemorrhage followed, and the hemoglobin fell from 81 per cent (13.5 Gm.) on December 27 to 72 per cent (12 Gm.) on January 3. The spleen could not be palpated on January 3, or thereafter.

The dose of penicillin was reduced to 3,000 units on January 7 and to 1,000 units on January 10, and the drug was discontinued on January 17. The small transfusions were continued to correct the anemia, and, on January 26, menstruation, which had been absent since April, re-

appeared. The patient was discharged on January 30, at which time she weighed 51.8 kg. She has continued to improve. On February 27, she reported her weight as 125 pounds (56.8 kg.), as compared with a normal weight of 130 pounds before her illness. On June 15, 1944, she
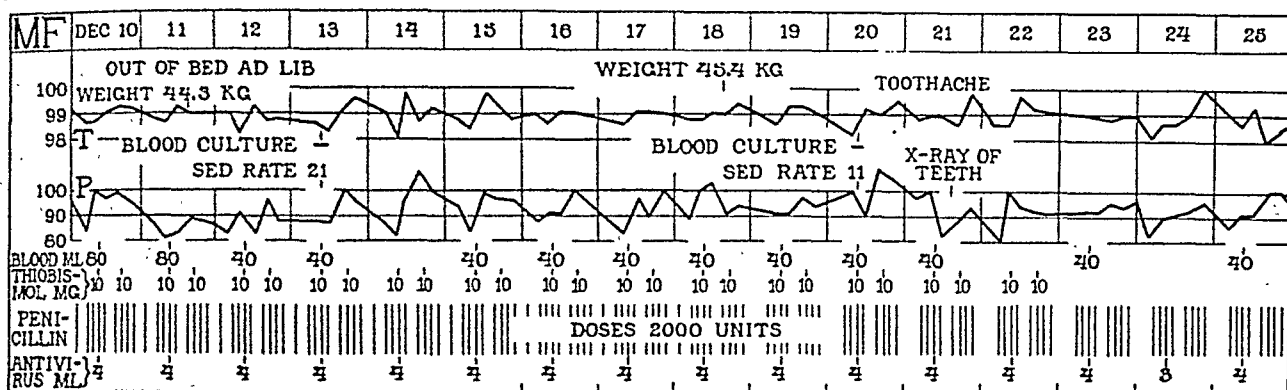
Fig. 15.
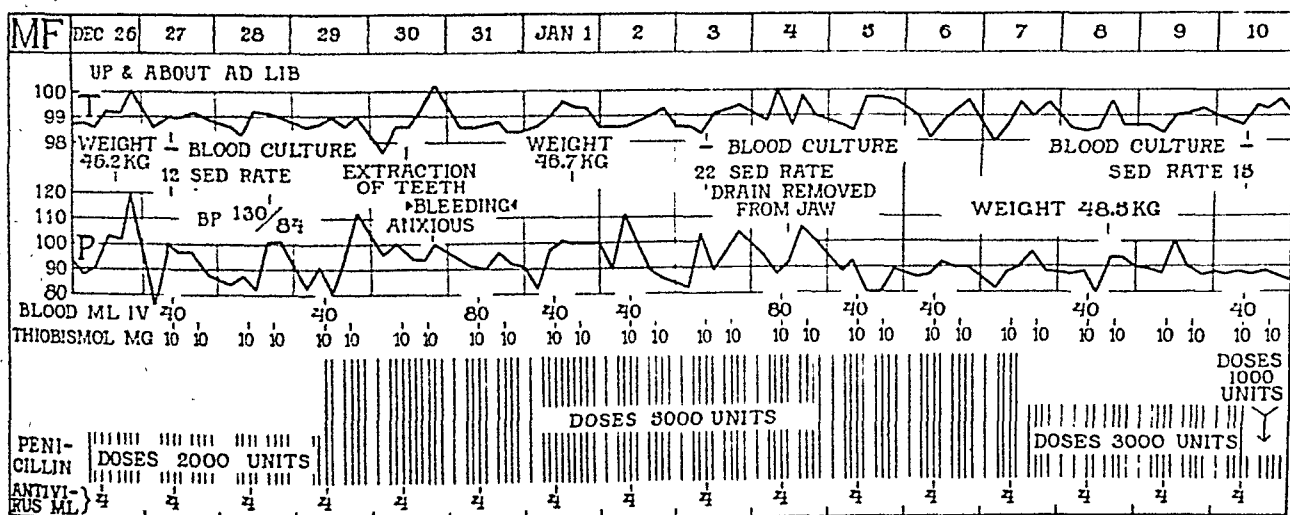
Fig. 16.
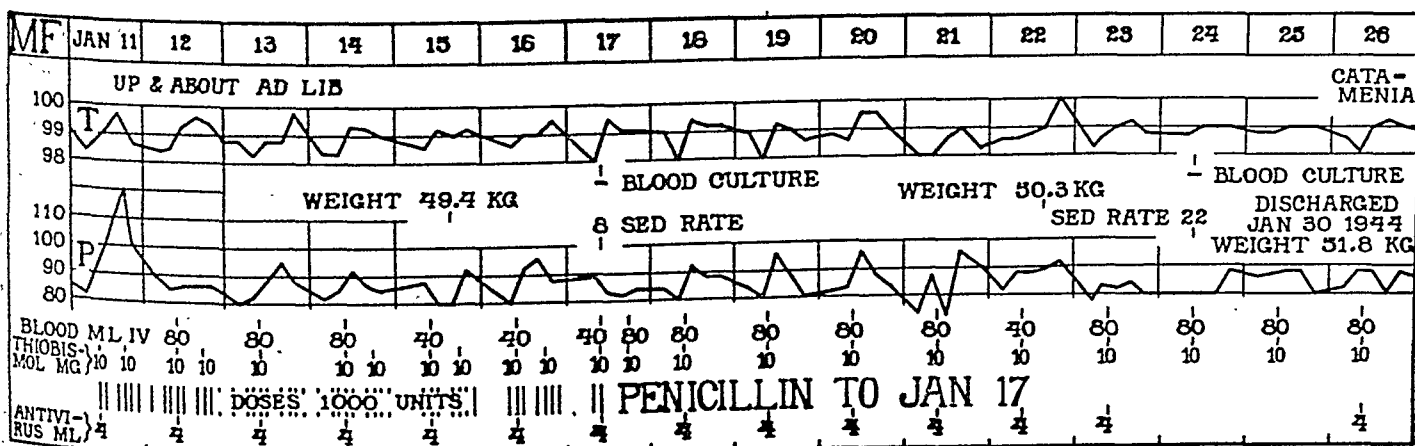
Fig. 17.

returned for examination. At this time she weighed 136 pounds (61.7 kg.), and had been restricting her diet to avoid becoming obese. The hemoglobin was 13 Gm. per 100 c.c. of blood; the erythrocyte count was 4,260,000, and the leucocyte count, 9,000. The blood pressure was 160/103. The patient ascribed the elevation of blood pressure to excite-

ment, and stated that her systolic pressure at home a few days before had been 128. The loud systolic mitral murmur was present as before. Her general appearance was excellent, and she was planning to go north with her family for a vacation of two months.

COMMENT

For the treatment of this patient there were expended approximately 4,864,000 units of penicillin, enough to terminate the active stage of inflammation in eighty cases of gonorrheal urethritis, an expenditure which may be deemed extravagant in the present emergency. We venture to suggest, however, that the morale of the men on foreign duty may be bolstered somewhat by the thought that the wife of a medical officer on duty overseas and the mother of his children has been given a chance to survive to greet him on his return. There has been some question concerning the use of the sulfadiazine, thiobismol, neoarsphenamine, antivirus filtrate, and citrated blood. These agents were not of themselves adequate to overcome the disease in this case. They were employed because they have seemed to exert a helpful influence in our previous experience with numerous patients, and especially because of the results of therapeutic tests in experimental endocarditis in animals.[6-19] Our purpose was not merely to demonstrate the value of penicillin, but rather to preserve the life of the patient, and to ensure, if possible, a long period of arrest in the activity of the infection. The record speaks for itself, and few will doubt the outstanding bacteriostatic effect of the penicillin, which was easily demonstrated in vitro as well as in vivo. We hope and believe that we have erred on the side of overtreatment, and, if the present state of arrest persists in this case, it will suggest that the therapeutic efforts were perhaps too elaborate.

Since improvement became evident in the case of M.F., there have come under our care fifteen more patients with endocarditis. Of these, there were nine in whom the infecting organism was *Str. salivarius*, or a closely related type of streptococcus. Two of these patients are dead; three are in the stage of clinical arrest and have been discharged from the hospital; four are still in the hospital under treatment or observation. The other six patients had endocarditis in different etiological categories. Of these, one is dead, two are in the arrested state and discharged, and three are still under care in the hospital. All the discharged patients have been returning at regular intervals for examination. We have not selected the cases, and no patient has been refused or excluded because of the advanced stage of the disease. In general, we consider the prognosis more favorable in young persons and in those who have been ill only a short time.

difficulties, by Rare Chemicals, Inc., of Flemington, New Jersey, and by Charles Pfizer and Company, Inc., of Brooklyn, New York. It is a peculiar pleasure to salute Mr. John L. Smith, Vice-President of Charles Pfizer and Company, who, because of his broad humanitarian vision and keen scientific interest in the problem, deserves to be designated as the Abou ben Adhem of modern therapeutic research in bacterial endocarditis.

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Abstracts and Reviews

Selected Abstracts

Shuler, R. H.: Kupperman, H. S., and Hamilton, W. F.: Comparison of Direct and Indirect Blood Pressure Measurements in Rats. Am. J. Physiol. 141: 625, 1944.

Simultaneous readings of systolic pressure of rats from the Williams, Harrison, Grollman apparatus and from direct arterial puncture showed that pressures obtained by them were too low and that the disagreement was variable. Addition of 40 ± 10.7 mm. Hg to published figures will bring them to about the right value.

Substitution of a 16 mm. cuff for the 40 mm. cuff or 26 mm. cuff gave readings which were consistently 36.5 ± 5.6 mm. Hg low, and which were less variable. A 5 mm. cuff gave much truer readings. They were accurate at 120 mm. Hg, but somewhat too high above that level, and too low below that level. These errors can be corrected. The use of a ½ mm. capillary tube for the oncometer gave sharper end points, greater reproducibility and eliminated the need of heating the rats and of training the observer.

<div align="right">AUTHORS.</div>

Patras, M. C., Brookhart, J. M., and Boyd, T. E.: Respiratory Effects on the Filling of the Ventricles During a Prolonged Diastole. Am. J. Physiol. 142: 52, 1944.

Ventricular volume was recorded by means of a cardiometer in the closed chest, the recording system being so arranged that external pressure on the ventricles followed the normal respiratory variations of intrathoracic pressure. Diastole was prolonged by vagal stimulation.

Under these conditions, ventricular filling at any stage of diastole is accelerated by inspiration and retarded by expiration. If either inspiration or expiration occurs while filling is in progress, the gradient of the filling curve is altered thereby. The volume curves thus very considerably in form. Such variations are particularly prominent during the stage of diastasis.

The effects described become less conspicuous as the mean level of venous pressure is raised, but are still demonstrable when venous exceeds intrathoracic pressure by 90 mm. of water.

<div align="right">AUTHORS.</div>

Holt, J. P., and Knoefel, P. K.: Changes in Plasma Volume and Cardiac Output Following the Intravenous Injection of Gelatin, Serum, and Physiological Saline Solution. J. Clin. Investigation 23: 657, 1944.

Plasma volume, arterial and venous oxygen content, oxygen consumption, arterial blood pressure, right auricular pressure, and the hematocrit were determined in normal barbitalized dogs, before and after the intravenous injection of 50 c.c. per kg. body weight of 0.9 per cent sodium chloride solution, gelatin solution, and serum. Blood volume, cardiac output, total peripheral resistance, and the oxygen content of 100 c.c. of arterial red cells were calculated.

Sodium chloride solution gave a small and brief increase in plasma volume. Gelatin solution and serum gave a greater and more sustained increase in plasma volume.

The injection of these solutions caused the cardiac output to increase and the total peripheral resistance to decrease.

No consistent quantitative relationship was found between blood volume and cardiac output, between blood volume and right auricular pressure, or between cardiac output and right auricular pressure.

Blood serum and a 3.75 per cent gelatin solution are about equally retained in the vascular bed, both to a greater extent than is 0.9 per cent sodium chloride.

AUTHORS.

Donovan, G. E.: Phono-Electrocardioscopy. Lancet 1: 500, 1944.

The author has designed an instrument for amplified auscultation, phonocardiography, electrocardiography, and sphygmography which he calls a phonoelectrocardioscope. The instrument permits: simultaneous, direct, continuous, visual recording of the phonocardiogram and electrocardiogram, plus amplified auscultation; simultaneous, direct, continuous, visual recording of the phonocardiogram and sphygmogram, plus amplified auscultation; simultaneous, direct, continuous, visual recording of a stethoscopic phonocardiogram and linear phonocardiogram of the same area plus amplified auscultation; simultaneous, direct, continuous, visual recording of the phonocardiogram of one area with that of another, plus amplified auscultation; simultaneous, direct, continuous, visual recording of any pair of the electrocardiographic leads, such as Leads I and III; observation for any length of time; detailed visual analysis. The reserve gain of the amplifiers and the wide range of time-base speeds make possible traces of any size considered desirable; photographic registration of the traces; accentuation of murmurs of desired sounds and attenuation of unwanted ones.

The instrument is described in detail and its advantages are pointed out. It should be useful in all forms of cardiology.

McCULLOCH.

Clagett, A. H.: The Electrocardiographic Changes Following Artificial Hyperpyrexia, Am. J. M. Sc. 208: 81, 1944.

While the majority of electrocardiographic changes following fever therapy are insignificant and probably due to the effect of tachycardia, it is possible to have changes due to severe myocardial damage, such as that caused by occlusion of a small coronary artery.

In those cases with myocardial damage due to fever, one should not give a good prognosis merely because the patient is young and the causative agent (fever) has been removed. The treatment of these cases should be the same as that given myocardial infarction due to any other cause.

AUTHOR.

Faulkner, J. M., and Duncan, C. N.: The Significance of Marked Left Axis Deviation of the Electrocardiogram. Am. J. M. Sc. 208: 205, 1944.

An attempt was made to correlate marked left axis deviation of the electrocardiogram with significant clinical and post-mortem findings. A study of the clinical records in two hundred cases revealed that 51.5 per cent had no underlying reason for, or evidence of, left ventricular enlargement.

Measurements of the heart from teleoroentgenograms in ninety-seven cases were within normal limits in thirty-five cases (37 per cent). In twenty-seven autopsied cases the heart was entirely normal anatomically in the older age groups.

AUTHORS.

Wenner, H. A.: Notes on Congenital Auriculo-Ventricular Dissociation: Report of a Case of Congenital Complete Heart Block. Connecticut M. J. 8: 160, 1944.

The clinical history of a 6-year-old girl with congenital heart block and Adams-Stokes attacks has been described. A résumé of the clinical and pathologic findings in congenital heart block has been presented.

AUTHOR.

Thomas, W. C., and Harrison, T. R.: The Effect of Artificial Restriction of Activity on the Recovery of Rats From Experimental Myocardial Injury. Am. J. M. Sc. 208: 436, 1944.

Following experimental injury to the hearts of rats the mortality is decidedly greater when the animals are kept closely confined in small cages which restrict muscular activity.

Animals so confined display considerably less activity, as measured by the work adder method, than control animals allowed to wander freely about in larger cages.

Observations with the optional treadmill have shown that following injury to the heart the rat tends to return to the preoperative level of exercise within a period of three to seven days.

Enforced strenuous muscular effort even when carried out within twenty-four hours after cardiac injury, did not materially increase the mortality in rats. Likewise, such exercise carried out in three or more days after the operation did not cause a significant increase in mortality.

The question of the desirability of prolonged and rigid rest in bed following myocardial infarction in patients has been discussed and it has been pointed out that this procedure has serious disadvantages as well as some advantages. On the basis of the available evidence it would appear that during the first two weeks the advantages of strict bed rest probably outweigh the disadvantages, but that after this time the reverse is probably true.

AUTHORS.

Wainwright, C. W.: Dissecting Aneurysm Producing Coronary Occlusion by Dissection of the Coronary Artery. Bull. Johns Hopkins Hosp. 75: 81, 1944.

A case of dissecting aneurysm is presented in which myocardial infarction was produced by dissection along the left coronary artery and its anterior descending branch. The lumen of the latter was occluded by the pressure of the hematoma within its wall. The clinical features of the case were those of both dissecting aneurysm and myocardial infarction. When typical signs and symptoms of both conditions are present, such a course of events as obtained here warrants clinical consideration and probably occurs with greater frequency than reports indicate.

AUTHOR.

Scott, G. E. M.: Rheumatic Infection in Childhood: A Survey From the Children's Hospital, Melbourne. M. J. Australia 2: 309, 1943.

Six hundred forty-five cases of rheumatic infection occurring at the Children's Hospital, Melbourne, are examined, and the mortality rate is shown. In contrast to most statistics, there is a small preponderance of male patients. The age incidence has been found to be slightly higher than the average. The question of

symptomatology and of the occurrence of carditis is discussed, together with investigational methods. Reference is made to the problem of treatment, and its importance is stressed.

AUTHOR.

Cornell, A., and Shookhoff, H. B.: Actinomycosis of the Heart Simulating Rheumatic Fever. Arch. Int. Med. 74: 11, 1944.

Involvement of the heart in actinomycosis is rare. Analysis of three new cases and of sixty-five others collected from the literature shows that the heart may be involved by direct extension of the infection from a neighboring organ (most commonly the lungs) or by metastasis through the blood.

Metastatic involvement rarely produces clinical signs. About half of the patients in whom involvement of the heart is by direct extension show clinical manifestations.

The most common clinical manifestation in cardiac actinomycosis is congestive heart failure. A pericardial rub was heard in three cases and cardiac murmurs in only two.

AUTHORS.

Holbrook, W. P.: The Army Air Forces Rheumatic Fever Control Program. J. A. M. A. 126: 84, 1944.

Acute rheumatic fever shows a striking geographic variation in its distribution, as indicated by the incidence rates per thousand troop population in the various geographic areas.

Acute rheumatic fever occurring in high incidence during this study in every instance has been preceded by a high incidence of hemolytic streptococcus infections.

A 50 to 75 per cent reduction in the incidence of respiratory diseases and streptococcic infections has been accomplished by the use of sulfadiazine prophylaxis under carefully controlled conditions and on a significantly large troop population. No serious drug reactions occurred.

From the partial data at hand, it appears that the reduction in rheumatic fever parallels that of respiratory and streptococcic diseases.

The possibility of utilizing these prophylactic methods, thus saving millions of hospital days, avoiding serious complications, and adding millions of effective man days to the war effort, should be given consideration.

AUTHOR.

Fox, T. T., and Bobb, A. L.: Cardiac Arrhythmias in 1,000 Cases of Pulmonary Tuberculosis. Am. J. M. Sc. 208: 201, 1944.

Pulmonary tuberculosis does not affect the incidence of abnormal cardiac rhythm or abnormalities in the conduction mechanism. In the majority of cases presenting these abnormalities, other clinical or laboratory evidence of intrinsic, cardiovascular involvement can be elicited.

It is suggested that right pulmonary lesions involving the mediastinum may constitute an extracardiac factor in the causation of arrhythmias and conduction abnormalities in a *previously* diseased myocardium.

AUTHORS.

Mosenthal, H. O.: Development of Hypertension Associated With Lesions of the Kidney. Am. J. M. Sc. 208: 210, 1944.

Unilateral renal disease may exist for many years without affecting the blood pressure. As compensatory processes for the maintenance of normal arterial tension became strained, periods of intermittent rise in blood pressure occur. Finally, a permanent hypertension may develop. The extirpation of a unilaterally diseased

kidney should prevent a rise in blood pressure, or remedy it if it has become permanently established, provdied there are no causes for hypertension either in the remaining kidney or elsewhere in the body.

<div align="right">AUTHOR.</div>

Thomas, C. B.: Experimental Hypertension From Section of Moderator Nerves: Relationship of the Acute Pressor Response to the Development and Course of Chronic Hypertension. Bull. Johns Hopkins Hosp. 74: 335, 1944.

The acute and chronic pressor responses are of similar magnitude and general character in a given animal.

A depressor influence usually appears within a few minutes of the maximal acute pressor response following moderator nerve section, which brings the pressure down to normal for a day or two and which may be present in some degree for several weeks.

Chronic hypertension usually appears within forty-eight hours after complete moderator nerve section, and disappears only if nerve regeneration occurs.

<div align="right">AUTHOR.</div>

Morton, B. M., Shearburn, E. W., and Burger, R. E.: Synthetic Vitamin K and the Thrombosis of Veins Following Injury. Surgery 14: 915, 1943.

A group of experiments performed to study the possible influence of vitamin K on thrombus formation in dogs has been described. The radial and saphenous veins of the legs of fifty-two dogs were traumatized mechanically by sacrifying the intima with a hooked needle. The veins were removed at forty-eight- and ninety-six-hour intervals afterwards. Twenty-seven of the animals received a surplus of synthetic vitamin K along with the regular diet for a week prior to the injury, and the remaining twenty-five were utilized as controls. Prothrombin times, hematocrit determinations, and clotting times were made in each animal at intervals, without any demonstrable effect of synthetic vitamin K administration.

The incidence of thrombosis after injury to the intima of the veins was not significantly increased coincident with the administration of synthetic vitamin K, being 33 per cent in the control group and 38 per cent in the vitamin K group. The small difference does not seem important. The prothrombin values, which are important in the coagulation process, did not significantly change after the administration of synthetic vitamin K. There was no significant difference in the results obtained by the Squibb and Abbott synthetic preparations. Those dogs with a hematocrit reading below 40 per cent, however, revealed a slightly higher incidence of thrombosis in both the control and vitamin K fed group.

Clinically, the incidence of thrombophlebitis has been less in the University of Virginia Hospital in the smaller group of women given vitamin K just before or at the time of delivery than in the larger group receiving no exogenous vitamin K except in the normal diet.

<div align="right">AUTHORS.</div>

Davis, B. D.: The Indirect Measurement of Mean Venous Oxygen Tension During Anoxia. J. Clin. Investigation 23: 666, 1944.

A method is presented for determining the mean venous oxygen tension ($MVpO_2$) indirectly by means of equilibrating gas mixture of low pO_2 with pulmonary arterial blood. Reproducible results were produced under standard but nonbasal conditions, ranging, in fifteen individuals, from 26 to 32 mm. Hg at atmospheric pressure.

Observations at simulated altitudes of 8,000 to 20,000 feet indicated that the cardiac output rose progressively with altitude, reaching 189 per cent of normal at 20,000 feet. This circulatory compensation decreased the tissue anoxia at the

various altitudes by 40 per cent, the MVpO₂ at 20,000 feet being 19.8 mm. rather than the value of 13.5 mm. which would have obtained if the cardiac output were constant.

<div align="right">AUTHOR.</div>

Bollman, J. L., and Flock, E. V.: Changes in Phosphate of Muscle During Tourniquet Shock. Am. J. Physiol. 142: 290, 1944.

The changes which occur in the phosphates of muscle, the blood supply of which has been completely occluded, are those of autolyzing muscle. Adenosine triphosphate almost disappears after three hours and phosphocreatine is almost completely hydrolyzed in one hour. The inorganic phosphates of the muscle rapidly increase to a maximum in about four hours. The total of the acid-soluble phosphates is not changed. If the flow of blood is restored to the muscle within three hours there is resynthesis of adenosine triphosphate and phosphocreatine with a corresponding decrease of the inorganic phosphate. Fatal shock does not develop even though large amounts of muscle have been occluded. When the occlusion is released after more than three hours there is no regeneration of adenosine triphosphate or phosphocreatine but considerable inorganic phosphate is washed from the injured muscle into the blood. Fatal shock develops in rats so treated if the muscles of more than one leg and thigh have been occluded for three and a half hours or if the occlusion of only one thigh and leg persisted for six hours before release. This type of shock is definitely not due to adenosine triphosphate washed out of the muscle because adenosine triphosphate is destroyed during the occlusion and its decomposition products appear to be relatively nontoxic. In rats surviving release after occlusion of one leg for four hours there is almost complete necrosis of the injured muscle but sufficient cells remain alive to restore themselves. After four to six weeks there is restoration of function of the leg, although the original size of the muscle bundles is not completely restored.

<div align="right">AUTHORS.</div>

Sherman, C. F., and Ducey, E. F.: Cardiac Mensuration. Am. J. Roentgenol. 51: 439, 1944.

A direct comparison was made between the transverse cardiac diameter of two hundred adult males, obtained within ninety days of death, and the weight of their hearts at autopsy.

In this study, the results by the Ungerleider method are much more closely correlated with the actual cardiac weight than are those of the other two roentgen methods studied.

There is constant correlation between the percentage deviation of the transverse diameter, as obtained by the Ungerleider method, and the percentage deviation in heart weight as calculated from Zeek's table. This correlation expressed numerically has a value of 1 to 3.3.

Marked deviation from normal body weight and pericardial effusion greater than 200 c.c. impair the accuracy of the method to such an extent as to preclude its use without qualification.

<div align="right">AUTHORS.</div>

Mazer, M., and Wilcox, B. B.: A Simple Graphic Method for Measuring the Area of the Orthodiagram. Am. J. Roentegnol. 51: 444, 1944.

A simple graphic method for the determination of the area of the orthodiagram is described. It requires no equipment not readily available to any physician. Its application to one hundred cases checked by the planimeter shows it to have a sufficiently high degree of accuracy for clinical purposes.

<div align="right">AUTHORS.</div>

Gage, I. M.: The Technical Simplicity of the Matas Endo-Aneurysmorrhaphy. Ann. Surg. 119: 468, 1944.

Endo-aneurysmorrhaphy is the surgical procedure of choice in treating aneurysms of the peripheral arteries. There are only two types of endo-aneurysmorrhaphy that are applicable to aneurysms of the peripheral arteries: The restorative (saccular) type; and the obliterative (fusiform) type. An adequate and sustained collateral circulation must be present and satisfactorily demonstrated before the operation is undertaken. The collateral circulation can be developed by two methods: Mechanical (Matas method), and physiologic (blocking out the sympathetics, the author's method). Absolute hemostasis must be obtained and continued until the intrasaccular toilet is completed. This operation is contraindicated in all arterial aneurysms in which the blood supply cannot be unequivocally controlled during the entire operation. It is the simplest of all surgical procedures used for the cure of arterial aneurysms.

AUTHOR.

Loewe, L., and Rosenblatt, P.: A New Practical Method for Subcutaneous Administration of Heparin. Am. J. M. Sc. 208: 54, 1944.

A simple, safe, and practical method for the subcutaneous administration of heparin has been devised. Its clinical application has been successfully attempted in fifteen cases of thrombophlebitis and phlebothrombosis.

With the technique of subcutaneous administration of heparin as here described, no instantaneous withdrawal of the heparin effect is as yet feasible. However, whole blood or protamine may be employed to neutralize the free heparin, while compression about the site of inoculation will effectively suspend its further liberation. This was demonstrated in a case of subacute bacterial endocarditis successfully heparinized by this method. Injections were made, as usual, in the lateral or anterior aspect of the thigh. Compression was effected for one to three hours by means of a tourniquet above or a compression cup about the site of injection. The use of this subcutaneous method of heparinization, while not yet commercially available, gives promise of sharply curtailing the cost of this anticoagulant agent because of the reduced heparin requirement and ease of administration.

AUTHORS.

Smull, K., Wégria, R., and Leland, J.: The Effect of Sodium Bicarbonate on the Serum Salicylate Level. J. A. M. A. 125: 1173, 1944.

When a serum salicylate level has been established and is being maintained by the oral administration of enteric coated tablets of sodium salicylate, the simultaneous administration of approximately equal amounts of sodium bicarbonate results in a definite fall of the serum salicylate level.

The simultaneous administration of equal amounts of sodium bicarbonate and enteric coated sodium salicylate prevents the establishment of as high a serum salicylate level as would be obtained with sodium salicylate alone.

AUTHORS.

Harrison, T. R.: Abuse of Rest as a Therapeutic Measure for Patients With Cardiovascular Disease. J. A. M. A. 125: 1075, 1944.

A review of some recent experimental evidence and certain clinical considerations leads to the following general conclusions:

Extreme restriction of body movement causes increased mortality in animals with experimental myocardial injury.

There is no proof that rest in bed carried out for many weeks after symptoms have disappeared is of value in the physical management of the patient with con-

gestive failure, angina pectoris, or myocardial infarction. The available evidence, while perhaps not conclusive, points to the contrary and more especially so if the recumbent posture is enforced while the patient is kept in bed.

From the psychic standpoint there is a definite disadvantage in the enforcement of a rigid regimen after the acute phase of the illness has subsided.

Until more definite information is available, the following tentative suggestions are offered for a plan of treatment which obviously requires modification according to the status of the individual patient:

a. Persons with congestive heart failure should be allowed out of bed for several hours a day, as soon as severe dyspnea at rest has subsided.

b. Following myocardial infarction, recumbency should not be prescribed for a longer period than two to three weeks after the more acute and alarming symptoms have subsided. The recumbent position should not be enforced on patients who are more comfortable sitting. Other things being equal, it would appear wise to allow elderly patients out of bed sooner than younger ones.

c. Rest in bed for more than a day or two at a time probably has no place in the treatment of angina pectoris except in those patients who are especially liable to develop myocardial infarction in the immediate future, as indicated by increasingly frequent and prolonged attacks at rest.

d. In all patients with the severe forms of heart disease, activity should be kept below the symptomatic threshold, i.e., should be less than that amount which induces dyspnea or pain.

AUTHOR.

Levine, S. A.:   Some Harmful Effects of Recumbency in the Treatment of Heart Disease. J. A. M. A. 126: 80, 1944.

Rest in bed, which has been the backbone of our treatment of heart failure, needs reconsideration in the light of some possible harmful effects.

There is both clinical and laboratory evidence to show that recumbency may be very harmful for certain patients with heart failure. The heart may be made to work more rather than less, and pulmonary congestion may be made worse rather than better at certain stages of heart failure by placing the patient in bed. Making the bed slant downward by placing 9-inch blocks of wood under the headposts is a simple method of minimizing this undesirable effect. At times it is wise to treat patients with heart disease in a chair rather than in bed.

Cardiac as well as noncardiac patients who are confined to bed for any appreciable length of time should be instructed to exercise their legs frequently or to have massage of the legs to prevent venous thrombosis of the legs and pulmonary emboli.

AUTHOR.

Erratum

In the September, 1944, issue of the JOURNAL, Vol. 28, p. 298, the article by R. M. Tandowsky, Norma Anderson, and J. K. Vandeventer, entitled "An Electrocardiographic and Clinical Study of Various So-Called Cardiac Drugs," should be corrected as follows: In Table I, page 299, the sixth line in the second column should read: 3 c.c., 1.5 cat units; the last line in the first column should read: Metrazol (Bilhuber-Knoll). On page 303, Digalin, on Fig. 7 should be Digalen. On page 306, Fig. 11, Metrazol should be followed by (Bilhuber-Knoll). On page 307, Fig. 13, Digalen should appear above the second tracing, and Scillaren above the third tracing.

American Heart Association, Inc.

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

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The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

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*Executive Committee.

Original Communications

SYNCOPE ASSOCIATED WITH EXERTIONAL DYSPNEA AND ANGINA PECTORIS

ABNER GOLDEN, M.D.

ATLANTA, GA.

IT IS well known that recurrent attacks of syncope occur in association with aortic stenosis and in disorders of the intracardiac conduction mechanism (Adams-Stokes syncope). Little attention has been paid, however, to the occurrence of syncope and periods of mental confusion in patients with other common forms of heart disease. Any type of heart disease that produces acute paroxysmal dyspnea and anginal pain may be associated with periods of unconsciousness.

As will be noted, the attacks of syncope experienced by the patients reported here were associated with both paroxysmal dyspnea and the appearance of characteristic angina pectoris. This syndrome was first described by Gallavardin,[1] who gave it the name "syncope anginosa." Patients with heart disease are usually limited in their activities by one of two factors. Either dyspnea appears when the left ventricle is unable to remove blood from the pulmonary circuit, or angina pectoris results from focal ischemia due to inability of the coronary arteries to supply an adequate amount of blood to the myocardium. Which symptom is the limiting factor during exertion depends on the relative efficiency of the myocardium and the coronary circulation. It is not uncommon for patients to have first one symptom, and then, at a later date, the other. This is particularly striking when angina pectoris disappears after myocardial infarction, and is supplanted by dyspnea as the limiting symptom. There are patients, however, in whom the coronary circulation and the ventricular output "fail" at the same level of exertion, and who complain of both dyspnea and angina pectoris. The cases under consideration fall into this group. The significance of these factors in the production of syncope will be discussed later.

CASE REPORTS

CASE 1.—W. E. W., aged 61 years in 1941, was admitted to the hospital because of anginal pain, syncope, and paroxysmal nocturnal dyspnea. In 1940, a year and a half before entry, he began to experience substernal and precordial pain, "knifelike" in character, produced by exertion, and relieved by rest and the administration of nitroglycerin. At about the same time, he noted frequent attacks of paroxysmal nocturnal dyspnea. Six weeks before admission, during exertion, he suddenly noted a "fluttering" of the heart, followed shortly by severe dyspnea and "drilling" precordial pain. A minute later he lost consciousness, and remained unconscious for several hours. He awoke feeling very "limp." During the six weeks before admission, he had experienced numerous similar attacks of angina, "fluttering," and dyspnea, produced by exertion, and followed by sudden syncope unless he was able to lie down or gain support. He also had many attacks of severe nocturnal dyspnea and angina, but no syncope.

Physical examination revealed a large, obese man with marked orthopnea. There were mild tortuosity and arteriovenous nicking of the retinal arterioles. There were a few moist râles at the bases of both lungs. The heart was slightly enlarged to the left. The sounds were of poor quality, and there was a grade 1 apical systolic murmur. The rhythm was normal. Marked hepatomegaly was present; the edge of the liver was palpable 10 cm. below the costal margin. The extremities and reflexes were normal. The blood pressure was 134/90. Carotid sinus stimulation and forced hyperventilation produced no abnormal effects.

The urine was normal except for 1 plus proteinuria on two occasions. The erythrocyte count was 6.2 million, with a hemoglobin content of 16.8 Gm. per 100 cubic centimeters. The sedimentation rate was normal. The blood Hinton and Wassermann reactions were negative. The leucocyte count was 9,600. The icterus index, total protein, nonprotein nitrogen, and bromsulfalein excretion were within normal limits.

Roentgenologic examination of the heart showed slight prominence of the left ventricle and tortuosity of the aorta. Electrocardiograms showed only T-wave inversion which was probably a digitalis effect.

Comment.—This patient experienced numerous attacks of exertional dyspnea, angina pectoris, and sudden syncope during the six weeks prior to hospital admission. He had had symptoms of heart disease for one and one-half years. The clinical diagnosis was arteriosclerotic heart disease and hepatomegaly of unknown origin.

CASE 2.—M. L. H., aged 38 years in 1943, was found to have a positive serologic test for syphilis in 1934. In June, 1939, she first noted attacks of exertional dyspnea, and angina pectoris characterized by "mashing" substernal pain radiating down the left arm. These attacks became more frequent, and she also noted orthopnea, paroxysmal nocturnal dyspnea, and intermittent edema of the ankles. She had experienced about fifteen attacks of syncope during this period. A typical attack was described as the sudden appearance of shortness of breath during exertion, followed by anginal pain. In a few seconds she would lose consciousness for a period of from five minutes to as long as an hour. When she regained consciousness, the substernal pain often persisted for five or ten minutes, but was much milder.

She always felt cold and clammy after an attack, and had vomited on several occasions.

Physical examination showed a well-developed and well-nourished Negro woman. The blood pressure was 110/80. The optic fundi and the lungs were normal. The heart was slightly enlarged to the left. No murmurs were heard and the rhythm was regular. The pulmonic second sound was louder than the aortic second sound. The liver was palpable 2 cm. below the costal margin. The extremities and reflexes were normal. Neither carotid sinus stimulation nor hyperventilation produced syncope.

The urinalysis was negative. The erythrocyte count was 4.2 million, with a hemoglobin content of 13.5 Gm. per 100 cubic centimeters. The sedimentation rate was 23 mm. per hour. The leucocyte count was 8,100.

Roentgenologic studies of the heart showed slight left ventricular enlargement. Electrocardiograms showed left axis deviation, a deep S_3, an inverted T_3, and a slightly elevated $S-T_4$.

Comment.—This patient gave a history of numerous attacks of dyspnea, angina pectoris, and prolonged unconsciousness, brought on by exertion during the four years before admission to the hospital. The clinical diagnosis was probable coronary ostial disease due to syphilitic aortitis.

CASE 3.—W. T. M., aged 57 years in 1942, was admitted to the hospital complaining of attacks of angina pectoris and syncope. Four years before admission he was found to have hypertension, and, shortly thereafter, he began to experience exertional dyspnea and paroxysmal nocturnal dyspnea. These symptoms became marked. About six months later, he started having attacks of angina pectoris and syncope. Dependent edema developed two months before entry. The patient claimed he had had "hundreds" of syncopal attacks associated with exertion. These attacks started with severe shortness of breath and a feeling of being "choked-up." In a few seconds, or, at most, a minute, he was seized by "stabbing" substernal pain radiating down both arms as far as the elbows. Then, "everything went black," and he would lose consciousness for a period of several minutes to as long as an hour. He was able to tell when syncopal attacks were imminent, and avoided injury by lying down quickly. Syncope had never occurred at night. It was always preceded by angina.

Physical examination revealed a well-developed, obese man with marked orthopnea. His blood pressure was 210/100. The retinal arterioles showed moderate arteriosclerotic changes, with arteriovenous compression, but no hemorrhages or exudates. The heart was enlarged to the left. There was a rough, grade 2, systolic murmur, heard best over the third left intercostal space, but heard well over the entire precordium. The murmur was not transmitted to the neck vessels. The aortic second sound was sharp, and louder than the pulmonic second sound. The edge of the liver was palpable two fingerbreadths below the costal margin. There was marked edema of the lower extremities.

The urine was normal. Blood studies showed an erythrocyte count of 4 million, with a hemoglobin content of 10.2 Gm., a sedimentation rate of 55 mm. per hour, and a leucocyte count of 5,200. The blood Kahn reaction was negative.

Fluoroscopic examination showed definite left ventricular enlargement and tortuosity of the thoracic aorta, but no areas of intracardiac calcification. The electrocardiogram showed only left axis deviation.

Prolonged carotid sinus stimulation produced transient syncope. There was marked hyperpnea before recovery of consciousness. He then complained of mild chest pain, and stated that he felt as if he had been unconscious for several hours. An electrocardiogram taken during carotid sinus stimulation showed complete auriculoventricular block and marked slowing of the auricular rate.

Hyperventilation produced mild anginal pain, but no syncope.

Comment.—The clinical diagnosis was hypertensive heart disease and generalized arteriosclerosis. The patient gave a history of many attacks of syncope, preceded by exertional dyspnea and angina pectoris. Although syncope could be produced by prolonged carotid sinus stimulation, this syncope was subjectively different from the attacks previously experienced.

CASE 4.—H. G. N., aged 58 years in 1942, began having exertional dyspnea and edema of the ankles in 1933. Shortly thereafter, he noted attacks of angina pectoris. Orthopnea appeared in 1934, and paroxysmal nocturnal dyspnea in 1937. Exertion usually produced shortness of breath. However, he was often forced to stop activity by angina without dyspnea, although the latter usually appeared shortly thereafter. The angina was described as a "knifelike" pain radiating from the substernal region to the left axillary line in the fourth intercostal space, and was relieved by rest or nitroglycerin. In 1937, the patient had a sudden attack of syncope which occurred while sitting. It was not preceded by dyspnea. He stated he was unconscious for twenty-four hours. After this he had five attacks of syncope associated with exertion. All occurred when his cardiac function was poor, as evidenced by marked exertional dyspnea and peripheral edema. The attacks started with sudden, severe dyspnea, followed by anginal pain. Syncope then occurred without warning. He would remain unconscious for a period of several minutes to several hours. On innumerable occasions he had attacks of sudden dyspnea and angina, and "felt funny all over," but prevented syncope by sitting down immediately.

He was seen in the hospital after three of these syncopal attacks. On these occasions he showed evidence of marked congestive heart failure, and was either comatose or irrational. The temperature remained normal, as did the leucocyte count and sedimentation rate. Electrocardiograms showed no evidence of myocardial infarction.

Physical examination in October, 1942, revealed a blood pressure of 240/140. There was marked peripheral arteriosclerosis, and the retinal arterioles showed moderate tortuosity and arteriovenous compression. The lungs were normal. The heart was at the upper limits of normal size. The rhythm was regular and no murmurs were heard. The abdomen was negative. All of the reflexes were normal. Carotid sinus stimulation was without effect. Forced hyperventilation produced only "tingling" of the extremities.

Roentgenologic examination of the heart showed an aortic configuration and a tortuous aortic arch. Electrocardiograms showed only an abnormality of the T waves which was probably a digitalis effect.

Comment.—This patient had hypertensive heart disease and generalized arteriosclerosis. He had had exertional dyspnea and angina pectoris for nine years. He had had one attack of sudden syncope unassociated with exertion or dyspnea, but after this had five attacks of acute exertional dyspnea, angina, and syncope.

CASE 5.—J. W. C., aged 64 years in 1942. At the age of 32 years, during extreme exertion, the patient was suddenly struck with severe precordial pain accompanied by a cold sweat and prostration. An hour later, the pain radiated down the left arm. It was sharp, "stabbing," and intermittent; numbness of the same area at times replaced the pain. These symptoms continued for about fifteen hours. Ever after this attack the patient complained of frequent attacks of severe substernal pain radiating down the left arm. At first they were produced only by exertion, but, during the several years preceding admission, they had occurred when sitting or lying down. The pain would last three to five minutes, and was relieved by rest. In 1942, the patient had five attacks of very severe paroxysmal nocturnal dyspnea, occurring at times when cardiac decompensation was most marked. He was awakened by "suffocating" dyspnea. He would sit up or try to walk to a window. Immediately, the sharp substernal pain would appear. It would last about five minutes, and often reappear after a few minutes. His body then felt "numb all over." He would have only partial recognition of his surroundings, and felt as if he were "dreaming," but he did not believe he had ever lost consciousness. This state would persist for about one hour. As he became mentally clear, the chest pain would occasionally reappear in milder form.

The patient gave a history of a penile lesion in 1902, and had received antisyphilitic treatment by mouth for four years.

Physical examination revealed moderate retinal arteriosclerosis. The neck veins were distended. The lungs were emphysematous, but no râles were heard. The apex impulse of the heart was in the anterior axillary line in the sixth intercostal space. The rhythm was regular, with a rate of 64. There was a soft, blowing systolic murmur over the entire precordium, and a high-pitched, grade 2, aortic diastolic murmur was heard. The blood pressure was 190/85. There were a Corrigan pulse, a capillary pulse, and marked suprasternal pulsations. The liver was palpable two fingerbreadths below the costal margin. There was slight edema of the ankles. The reflexes were normal. Carotid sinus stimulation produced only slight slowing of the ventricular rate. Hyperventilation resulted in numbness and tingling of the extremities after a short time.

The urinalysis was negative. The hemoglobin content of the blood was 15 Gm. per 100 c.c., and the leucocyte count was 7,000. The blood Kahn reaction was positive.

Roentgenologic examination of the heart showed an aortic configuration, with marked left ventricular enlargement and tortuosity of the aortic arch. Electrocardiograms showed left axis deviation, slurred QRS complexes. a deep S_2 and S_3, and an inverted T_4.

Comment.—The clinical diagnosis was syphilitic aortitis with aortic regurgitation. Although this patient had never experienced actual syncope, he had had five attacks of severe paroxysmal nocturnal dyspnea, with angina pectoris, and marked loss of mental clarity.

CASE 6.—R. L. C., aged 54 years in 1942, had recurrent attacks of acute rheumatic fever as a child, and a further attack of polyarthritis at the age of 35 years. He had had exertional dyspnea for about one year, slight edema of the ankles for eight months, and orthopnea and paroxysmal nocturnal dyspnea for two months. Six months before he was seen, he began having substernal pain radiating to both shoulders and down the left arm, brought on by exertion. These attacks, always preceded and accompanied by marked dyspnea, were associated with "the staggers" and a "faint feeling" lasting about five minutes. He had had no syncope.

Physical examination showed moderate arteriosclerotic changes in the retinal arterioles. The anteroposterior diameter of the chest was increased, with moderate kyphosis. The apex impulse of the heart was in the anterior axillary line in the fifth left intercostal space. A grade 3 systolic murmur and a grade 2 diastolic murmur were heard at the apex. The rhythm was regular, except for occasional extrasystoles, with a rate of 60. The blood pressure was 110/65. There was no peripheral edema. Carotid sinus stimulation and forced hyperventilation produced no abnormal responses.

Fluoroscopic examination of the heart showed left and right ventricular enlargement and dilatation of the left atrium. There was calcification of the mitral valve. Electrocardiograms showed left bundle branch block, with inverted T waves in Leads I, II, and IV.

Comment.—The clinical diagnosis of rheumatic heart disease, with marked mitral stenosis and regurgitation, was confirmed by autopsy in June, 1943. In addition, there were moderate aortic stenosis and slight involvement of the tricuspid valve. Although this patient had never experienced syncope, he had had numerous attacks of dizziness and faintness associated with marked dyspnea and angina pectoris.

DISCUSSION

These patients present certain features in common. The sequence of events leading to syncope was described by them in remarkably the same manner. There was first the appearance of severe dyspnea, almost always associated with exertion. This was followed by true anginal pain, and then, in a matter of seconds, by syncope, unless the patient was able to sit or lie down immediately. This sequence was the same in those patients who described periods of marked impairment of cerebral function, although they did not experience actual syncope. Another feature was that syncope or mental confusion was most likely to occur at times when cardiac decompensation, as judged by exertional dyspnea and peripheral edema, was most marked.

The cause of the heart disease in these patients was varied. The clinical diagnoses were: arteriosclerotic heart disease, coronary ostial disease due to syphilitic aortitis, hypertensive heart disease (two cases), syphilitic aortic regurgitation, and rheumatic heart disease with mitral, and to a lesser degree, aortic stenosis and insufficiency. Varying degrees of congestive heart failure were found at the time of examination. Forced hyperventilation failed to produce syncope in any of the

cases. Carotid sinus stimulation was also without effect, except in Case 3. Here, transient syncope was produced, and electrocardiograms showed complete auriculoventricular block, but the patient stated that this attack was not similar to his previous syncopal attacks. Electrocardiographic studies of the other patients failed to reveal irregularities of rhythm or pacemaker.

The explanation of the periods of unconsciousness in this group of patients is not clear. It might be useful to review some of the common forms of syncope, and to consider these patients in their light.

SYNCOPE OF REFLEX ORIGIN

Syncope can be produced by several reflex mechanisms. The common faint, the syncope caused by certain types of neurogenic heart block, and the mental confusion and syncope secondary to hyperventilation are all reflex in origin.

Fainting occurs in patients with unstable vasomotor centers. The afferent stimuli may arise from the eyes, ears, or nose, from any afferent nerve in the body, or from the emotional content of thought. The efferent limb of the reflex arc may cause syncope by a marked decrease in arterial pressure secondary to either venous pooling or arteriolar dilatation, or, more rarely, by ventricular standstill secondary to sinoauricular or auriculoventricular block. In certain cases, both afferent and efferent limbs of the reflex arc are in the vagus nerve (so-called vagovagal syncope). The afferent impulses, which may arise in the pharynx, the bronchial mucosa, the esophagus, the stomach, and the mediastinum, cause syncope by sinus bradycardia or by sinoauricular and auriculoventricular block.

Was the syncope in the cases reported here similar to that of the common fainting attack? Patients who faint frequently give a history of previous attacks of syncope. Maloney,[2] in a study of syncopal attacks in blood donors, has pointed out that persons with a history of fainting are much more likely to lose consciousness than those who give no history of previous faints. Fainting is much more likely to occur when the patient is standing still than when he is active. The patients with heart disease described here gave no history of fainting before the onset of cardiac decompensation, and the loss of consciousness was precipitated by activity rather than quiet standing. In several cases the unconsciousness lasted for a longer period of time than is usual in simple fainting. Nevertheless, the ischemic myocardium, the congested lungs, and the great veins offer a source of many afferent impulses which might easily precipitate syncope, either by a depressor action on the arterial pressure or by reflex cardiac standstill.

Syncope due to a hyperactive *carotid sinus* reflex is a well-known phenomenon. As pointed out by Weiss,[3] this may occur in three ways:

(1) Stimulation of the sinus may result in reflex slowing of the heart rate and a fall in blood pressure secondary to decreased cardiac output, comparable to Adams-Stokes syncope. This reflex can be abolished by atropine and by epinephrine and ephedrine. (2) There may be a direct fall in arterial pressure, independent of the heart rate. This mechanism is abolished by increasing the peripheral vascular tone with epinephrine or ephedrine, but is not affected by atropine. In both of these types, syncope can be attributed to cerebral "ischemia," or the rapidity of change in cerebral blood flow. (3) Syncope may occur without either a fall in blood pressure or slowing of the heart rate, and with no change in peripheral blood flow per se. This is apparently due directly to cerebral components of the reflex arc.

The appearance of syncope in cases of aortic stenosis has been attributed to involvement of the carotid sinus reflex. Marvin and Sullivan[4] pointed out that syncope was almost always associated with exertion, although the exertion was often quite mild. This relation to exertion and the long duration of the unconsciousness, they felt, ruled out the common faint and some of the common cardiac arrhythmias. One of their patients showed transient auriculoventricular nodal rhythm, ventricular premature contractions, and auricular tachycardia during induced syncope. They hypothesized that increased pressure within the carotid artery secondary to exertion could sufficiently stimulate the carotid sinus to cause reflex syncope, and that the electrocardiographic changes observed in this case were consistent with this form of syncope. Unfortunately, the carotid sinus reflex was not tested in their five cases, and Contratto and Levine[5] were unable to demonstrate abnormal sensitivity of the carotid sinus in nineteen cases of aortic stenosis.

All of the patients under discussion were tested for carotid sinus sensitivity. In one instance (Case 3), prolonged stimulation resulted in transient syncope, and electrocardiograms showed complete auriculoventricular block and slowing of the auricular rate. However, this induced syncope was subjectively unlike the spontaneous attacks he had previously experienced. In none of the other cases was there any significant slowing of the heart rate, or dizziness, weakness, or syncope.

Syncope is sometimes seen as a symptom of *hyperventilation*. It usually occurs while the patient is standing or sitting. It is prevented rather than precipitated by exercise. In this syndrome there is a disturbance of cerebral metabolism that is probably due to a combination of decreased cerebral blood flow secondary to orthostatic pooling of blood, and alkalosis.[6]

This type of syncope is readily diagnosed by reproduction of the symptoms during forced hyperventilation. All of the patients under discussion were subjected to this procedure and in no instance did syncope occur.

INABILITY OF THE HEART TO INCREASE THE CARDIAC OUTPUT
NORMALLY IN RESPONSE TO EXERTION

It is possible that the syncope of these patients was the result of inability of the failing heart to increase its output normally during exertion. The opening up of a large arteriolar bed in the extremities as the result of exercise, without a corresponding increase in cardiac output, might precipitate a fall in arterial pressure with resulting cerebral ischemia and loss of consciousness. This is an interesting theoretical possibility, but there is no experimental evidence to support it. An attempt was made to test this hypothesis on two patients with aortic stenosis and attacks of syncope. After the patients became compensated, the vascular bed in the lower extremities was dilated by occluding the arterial inflow for fifteen minutes. There was no abnormal fall in arterial pressure when the tourniquets were released and blood entered the dilated vessels of the lower extremities. These experiments are not conclusive because cardiac function was much better than at the time when syncope was experienced.

CARDIAC ARRHYTHMIAS AND ADAMS-STOKES SYNCOPE

Paroxysmal cardiac arrhythmias, particularly paroxysmal auricular tachycardia and bradycardia, are at times accompanied by syncope. Paroxysmal auricular fibrillation and transient ventricular fibrillation are less commonly encountered. There is no evidence that any of these phenomena played a part in the syncope of the patients reported here.

In true Adams-Stokes syncope of nonreflex origin, attacks are caused either by a changing ventricular pacemaker in the presence of complete heart block, or by changing degrees of block with a shift in pacemaker from the sinoauricular to the auriculoventricular node. These attacks bear no apparent relation to exertion or to the position of the body.

It must be stressed that the mechanism of the syncope in the cases reported here is not understood. It may well be that several of the factors that have been discussed were involved. Inability of the heart to increase the cardiac output during exertion, and reflexes arising from engorged lungs and an ischemic myocardium would seem to be a reasonable working hypothesis. The question arises as to whether anginal pain is a necessary part of the syndrome described. As far as could be ascertained from the histories, these attacks of syncope were, in many respects, similar to those which occur with aortic stenosis. Many patients with aortic stenosis have attacks of syncope unaccompanied by angina. It would appear fair to assume that pain is not necessary for the production of syncope of the type discussed here, but that its presence may act as a precipitating factor.

Many more detailed observations are needed before a definite answer can be reached. All attempts to reproduce syncope in this group

met with failure. This can be explained, at least in part, by the unwillingness of the patients to exercise to the point of onset of symptoms, and the fact that their cardiac function was improved by therapy before the attempt to induce syncope was made. It remains for critical clinical, electrocardiographic, and perhaps electroencephalographic observations to be made by physicians who are able to see similar patients during attacks of unconsciousness.

SUMMARY

Cases of syncope associated with exertional dyspnea and angina pectoris have been presented. Several of the common types of heart disease are included in the group.

The patients described in remarkably the same manner the sequence of events leading to syncope. Syncope was always preceded by both exertional dyspnea and angina, and was prone to occur at times when congestive heart failure was most marked.

Physical examination failed to reveal anything other than the usual features of the underlying disease. With one exception, carotid sinus stimulation and hyperventilation produced no abnormal responses.

The various common types of cardiovascular syncope have been considered in connection with these patients. The cause of their syncope remains obscure, but it is suggested that exertion beyond the capacity of the cardiac output and reflexes arising from engorged lungs and an ischemic myocardium may be important factors.

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A SUGGESTION FOR IMPROVING THE STRUCTURE OF THE CARDIAC CORONARY CIRCULATORY SYSTEM WITHOUT SURGICAL INTERVENTION

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IT IS common knowledge among physicians in Puerto Rico that, among the poor classes in the rural mountainous sections of the island, anemia, due to an incidence of uncinariatic infestation of over 80 per cent, associated with a marked protein and vitamin deficiency in their diet, is so prevalent that it constitutes their most constant and significant medical characteristic.

After working for four years in these rural, mountainous regions, I have been able to observe in the inhabitants another medical characteristic, just as significant as their anemia, namely, extraordinary hearts.

There is nothing more astonishing and puzzling than to observe, for the first time, one of these very anemic peasants walking several miles up and down hills with extreme ease. One would never imagine that it could be possible for any heart to stand, with ease, the enormous double strain of severe anemia and such violent exercise. The stair test for cardiac functional efficiency used by cardiologists in cities appears insignificant by comparison. But one continues to see this so frequently, day after day, that it soon ceases to appear extraordinary. Otherwise, we could not explain why it has not been mentioned repeatedly in our local medical literature during the last half century.

Furthermore, among 1,565 white, poor patients, over 45 years of age, from these rural areas, observed in my general medical practice during these four years, there was not a single case of angina pectoris due to coronary disease, whereas, among 453 white, well-to-do patients, over 45 years of age, also observed in my practice during the same four years, there were five deaths from coronary disease and its complications.

Of course, angina pectoris does not necessarily mean coronary disease. It is only the clinical expression of acute myocardial anoxia. The heart muscle develops, on exertion, acute oxygen want, and this is manifested by precordial pain; this occurs whenever there is partial obstruction of the coronary arteries and its muscle fibers are unable to receive additional blood with the necessary additional oxygen (ischemic anoxia), or when its muscle fibers are unable to receive additional hemoglobin with the necessary additional oxygen (anemic

anoxia).[1, 8, 10, 14, 15] Since not all of the hearts were examined when they had already developed a compensatory mechanism for anemia, as will be shown later, it is obvious that, among the large number of anemic patients studied, we have naturally seen some with precordial pain, with or without radiation, of short duration and induced by effort, but always in relation to anemic anoxia, and not to ischemic anoxia, and always disappearing spontaneously and completely as the anemia diminishes.

We must accept the fact that this represents a very limited series of cases, and that they have not been thoroughly analyzed. But the vital statistics of the Department of Health of Puerto Rico,[2] which are the only ones available, tend to corroborate the above to some extent. They show that the death rate from cardiac diseases is very much lower in the rural districts than in urban centers of the island. Nevertheless, these vital statistics do not help enough, because they include the mortality from all the diseases of the heart, whereas we refer exclusively to coronary disease. They also include the entire rural zone of the island, whereas we refer only to a special limited rural district where uncinariasis and anemia predominate enormously.

We are able to see, at least, that, in my limited personal experience, there appeared two clinically very significant and distinct groups of cases: One in which the patients rarely develop symptoms or die of coronary heart disease and its complications; the other, in which patients suffer and die of this condition at the usual rate.[18]

The two groups belong to the same race (white Puerto Ricans), are of approximately the same age (over 45 years), and live in the same geographical environment (1,500 to 2,500 ft. above sea level). They differ fundamentally in that the first group are very poor, live in the rural area, own very few latrines, walk barefooted, suffer an incidence of uncinariatic infestation of over 80 per cent, have a diet deficient in proteins and vitamins, and have the habit of nursing their children for a prolonged period of time. All these are factors that contribute to make anemia so prevalent in this group.

The other is a well-to-do group; they live in the urban zone, have toilets, wear shoes, seldom suffer from uncinariasis, have a more abundant and balanced diet, have lost the habit of prolonged nursing of their children, and, therefore, have no tendency to suffer from anemia with unusual frequency.

Anemia appears to be the prevailing and, possibly, the fundamental factor that, paradoxically, seems to exert a beneficial effect on the hearts of these country folk. Is it that anemia tends to prevent coronary sclerosis? Among these folk when they are over 45 years old, it is not rare to find evidence of sclerotic changes in the peripheral, retinal, cerebral, and renal arteries. If sclerotic changes are not uncommon in the rest of the arterial tree of these peasants after the age

of 45 years, it is to be expected that coronary sclerosis should also occur with some frequency among them. What actually happens is that when they suffer from coronary disease they do not tend to develop symptoms or to die from its complications with the usual frequency.

We see, then, that these country folk, among whom anemia is so prevalent, tend to possess extraordinary hearts:

1. Because of the unusual frequency with which they show extraordinary cardiac functional efficiency in the presence of severe anemia.

2. Because of their ability to tolerate silently (without symptoms) the coronary sclerosis that they may develop.

3. Because they so rarely die from the complications of coronary sclerosis.

Therefore, we came across clinical evidence suggesting most emphatically that, paradoxically, there may exist a so far unmentioned cardiologic phenomenon, namely, *anemia may exert a beneficial effect on the heart.*

In order to analyze this phenomenon without help, and without being able to transport to the mountains of Puerto Rico the necessary hospital facilities, with clinical, electrocardiographic, and radiologic laboratories, we had to apply an easy method that would give objective data as to how the individual heart reacts to anemia. It could not require any more instruments than a stethoscope and a hemoglobinometer, the only ones available.

Therefore, we started to look carefully into the so-called hemic murmurs, the physical sign to which little attention is paid in modern cardiology.[16] The accepted physiopathologic explanation is that these so-called hemic murmurs are not produced by any physical change in the blood that may be induced by anemia, but that they are due exclusively to weakness and dilatation of the cardiac muscle caused by the anoxemia induced by the anemia.[3] Naturally, when the cardiac muscle dilates, not only do the edges of the valves become separated, but the papillary muscles are also displaced, the chordae tendineae are unable to stretch sufficiently to permit perfect closure of the valves, and hemic murmurs are produced by functional valvular regurgitation. Like all regurgitative murmurs, these hemic murmurs are systolic if the dilatation occurs in the mitral or tricuspid valves, and diastolic if the dilatation affects the aortic or pulmonary openings.[3, 11, 16]

As a matter of fact, the dilatation occurs most frequently in the mitral or tricuspid openings, and, therefore, the hemic murmurs are almost always systolic. They lack any acoustic characteristic by which they could be identified. In the beginning, in cases of moderate anemia, they tend to be soft and localized. But when they progress with more severe anemia, they tend to become just as rough and loud, and to be transmitted just the same, as any other organic murmur.

The only thing that identifies these hemic murmurs is their fluctuations in direct proportion to the variations in severity of the anemia.

Therefore, because of their etiology, instead of hemic murmurs they should be called functional murmurs of myocardial anemic anoxia.

Then they assume their real clinical significance, for they are a very important objective sign of cardiac weakness induced by anemic anoxia, and, therefore, they may be used as an index of the ability of the heart to withstand anemia. In other words, a heart that develops hemic murmurs with a low-grade anemia must necessarily be weaker than another that tolerates this same degree of anemia without developing hemic murmurs. By the same token, a heart that is able to withstand severe anemic anoxia without developing hemic murmurs must be an extraordinarily good one.

We decided, therefore, to utilize this index of hemic murmurs in an attempt to obtain some objective evidence that would add or subtract weight to our clinical observations. Thus, we proceeded carefully to correlate the presence or absence of hemic murmurs with the hemoglobin level in poor patients over 2 years of age, with apparent anemia, from the mountainous rural districts.

In order to eliminate organic regurgitative murmurs, we excluded from the series all anemic patients with serologic or clinical evidence of syphilis and with active, or with a past medical history suggestive of, rheumatic infection.

Since the heart may be weakened and dilated not only because of anemic anoxia, but also, and mainly, by toxic infectious states, hyper- or hypothyroidism, and in beriberi, we also excluded all anemic patients with clinical evidence of the above mentioned conditions.

To eliminate as far as possible other nonanemic functional murmurs, we examined all patients in the erect posture.

To eliminate cardiopulmonary murmurs, we always made sure that the hemic murmurs persisted during apneic periods. The Tallqvist scale was used uniformly. All of the hemoglobin estimations and the auscultation were done personally in every case, so that any error would be constant and would not affect considerably the comparative value of the figures obtained in the series.

Our series, thus obtained, consists of 833 patients with apparent anemia, of which only 187, or 22.4 per cent, had hemic murmurs. In other words, approximately only one of every five anemic peasants studied had hemic murmurs, an incidence much lower than would be generally expected. We have not been able to find in the literature available in the library of the School of Tropical Medicine of Puerto Rico any similar analysis of the incidence of hemic murmurs, but only general impressions to the effect that they occur with such great frequency in anemic states that they do not deserve any commentary.[16]

The preceding discussion tends to corroborate objectively our clinical observation that the hearts of the peasants from the mountains of Puerto Rico, among whom uncinariasis and anemia are so prevalent, tend to be extraordinary, in most of the cases, because of their ability to compensate and preserve functional efficiency in the presence of apparent anemia without weakening, dilating, or developing hemic murmurs.

Table I shows the distribution of the cases and of patients with hemic murmurs at different levels of anemia.

TABLE I

GRADE OF ANEMIA	HB. (%)	TOTAL NUMBER OF CASES	TOTAL NUMBER OF PATIENTS WITH HEMIC MURMURS	INCIDENCE OF HEMIC MURMURS (%)
Moderate	60	320	60	18.4
Severe	50	422	82	19.2
Very severe	40	74	28	39.2
Extreme	30	17	17	100.0

It shows the direct relation between the increase in severity of the anemia and the increase in frequency with which hemic murmurs occur. Naturally, the more severe the anemic anoxia, the more difficult it is for the heart to compensate, and the more frequent the occurrence of the hemic murmurs. It also shows that the heart is able to compensate only to a certain extent, and, whenever the anemic anoxia exceeds this limit, 100 per cent of the hearts grow weak, dilate, and develop hemic murmurs.

Table II shows the distribution of cases and the incidence of hemic murmurs among patients under 30 years of age and those 30 years of age and over.

TABLE II

AGE	TOTAL NUMBER EXAMINED	TOTAL NUMBER WITH HEMIC MURMURS	PERCENTAGE WITH HEMIC MURMURS
Under 30 years	639	158	24.7
30 years and over	194	29	14.9
Total	833	187	22.4

The percentage of patients with hemic murmurs in the younger group, who would be expected to have better hearts, is distinctly higher than in the older group, who would be expected to have weaker hearts. This suggests that these peasants do not inherit, or are not born with, unusual hearts which are capable of tolerating anemia exceptionally well, but that their hearts probably develop a special compensatory mechanism for anemia during their lifetime. The older the person, the more the opportunities for acquiring uncinariasis and anemia, and the more frequently the compensatory mechanism for

anemia will tend to develop, with a smaller incidence of hemic murmurs. It also shows that older hearts, after developing some sort of a special compensatory mechanism for anemia, are more capable of withstanding anemic anoxia than supposedly stronger, younger hearts that have not yet developed this special compensatory mechanism.

TABLE III

AGE	TOTAL CASES	NUMBER POSITIVE WITH HEMIC MURMURS	PERCENTAGE POSITIVE WITH HEMIC MURMURS	TOTAL CASES	NUMBER POSITIVE WITH HEMIC MURMURS	PERCENTAGE POSITIVE WITH HEMIC MURMURS	TOTAL CASES	NUMBER POSITIVE WITH HEMIC MURMURS	PERCENTAGE POSITIVE WITH HEMIC MURMURS	TOTAL CASES	NUMBER POSITIVE WITH HEMIC MURMURS	PERCENTAGE POSITIVE WITH HEMIC MURMURS
	60% HB.			50% HB.			40% HB.			30% HB.		
Less than 30 years	244	49	20.0	320	68	21.0	58	24	41.3	17	17	100
30 years and over	76	11	14.4	102	14	13.7	16	4	25.0	--	--	--
Total	320	60	18.8	422	82	19.4	74	28	37.8	17	17	100

TABLE IV

AGE (YEARS)	TOTAL CASES	TOTAL CASES WITH HEMIC MURMURS	INCIDENCE OF HEMIC MURMURS (%)	TOTAL CASES	TOTAL CASES WITH HEMIC MURMURS	INCIDENCE OF HEMIC MURMURS (%)	TOTAL CASES	TOTAL CASES WITH HEMIC MURMURS	INCIDENCE OF HEMIC MURMURS (%)	TOTAL CASES	TOTAL CASES WITH HEMIC MURMURS	INCIDENCE OF HEMIC MURMURS
	60% HB.			50% HB.			40% HB.			30% HB.		
10 to 19	146	28	19.1	182	46	25.2	21	11	52.3	4	4	100
40 to 79	35	1	2.8	75	6	8.0	10	3	30.0	-	-	--

Table III shows the incidence of hemic murmurs in relation to age and severity of the anemia. It shows that the incidence of hemic murmurs is maintained distinctly higher in the younger than in the older group at all hemoglobin levels. This tends to corroborate and add weight to the deductions derived from Table II.

Table IV shows the incidence of hemic murmurs at different hemoglobin levels in two groups of patients who were more distinctly and widely separated in age. Again we see even more clearly the distinct tendency for hemic murmurs to occur more frequently among the younger patients and that this tendency is maintained constantly at the different hemoglobin levels.

Table V, from which all previous ones were constructed, shows the distribution of cases according to age, grade of anemia, and presence or absence of hemic murmurs.

TABLE V

AGE (YEARS)	HEMIC MURMURS	HB. 30%	HB. 40%	HB. 50%	HB. 60%	TOTAL
Less than 10	+	11	8	8	4	31
	−	0	17	59	28	104
	Total	11	25	67	32	135
10 to 19	+	4	11	46	28	89
	−	0	10	136	118	264
	Total	4	21	182	146	353
20 to 29	+	2	5	14	17	38
	−	0	7	57	49	113
	Total	2	12	71	66	151
30 to 39	+	0	1	8	10	19
	−	0	5	17	29	51
	Total	0	6	25	39	70
40 to 49	+	0	1	3	1	5
	−	0	3	30	15	48
	Total	0	4	33	16	53
50 to 59	+	0	1	2	0	3
	−	0	0	27	10	37
	Total	0	1	29	10	40
60 to 69	+	0	1	0	0	1
	−	0	4	8	6	18
	Total	0	5	8	6	19
70 to 79	+	0	0	1	0	1
	−	0	0	4	3	7
	Total	0	0	5	3	8
80 and over	+	0	0	0	0	0
	−	0	0	2	2	4
	Total	0	0	2	2	4
Total	+	17	28	82	60	187
	−	0	46	340	260	646
	Total	17	74	422	320	833

From Table V we can pick out different groups that are still more suggestive because of the marked contrast among them, for instance:

Group I.—This group includes 32 youths under 20 years of age, all with only moderate anemia (60 per cent Hb.), and yet all had hemic murmurs.

Group II.—This group includes 27 youths of approximately the same age, under 20 years, but with very severe anemia (40 per cent Hb.), and yet none of them had hemic murmurs.

Group III.—This group includes 41 elderly persons, all over 50 years old, all with severe anemia (50 per cent Hb.), and yet none had hemic murmurs.

Group IV.—Includes 11 persons over 70 years of age, with moderate to severe anemia (60 per cent to 50 per cent Hb.), and yet none had hemic murmurs.

Hence, either the accepted physiopathologic explanation of the so-called "hemic murmurs" is wrong, and there is some other factor in their pathogenesis besides weakening and dilation of the heart induced by myocardial anoxia, or we must admit that the heart is capable of

developing some sort of special compensatory mechanism whenever obliged to do so by anemia. If we accept the latter view we must also accept, as within the realm of reasonable possibilities, the following deductions and generalizations derived from the different tables:

1. The normal heart is so sensitive to anemic anoxia that even strong, youthful hearts are weakened, become dilated, and develop hemic murmurs in the presence of even moderate anemia (60 per cent Hb.).

2. That anemia compels the heart to develop a special compensatory mechanism that allows it to stand the anoxia induced by the anemia up to a certain limit, without weakening, dilating, or developing hemic murmurs.

3. That whenever a heart develops this special mechanism to its maximum, it is capable of tolerating even the anoxia of very severe anemia (40 per cent Hb.) without weakening, dilating, or developing hemic murmurs.

4. That this special compensatory mechanism tends to have a limit, and when the anemia becomes extreme (30 per cent Hb.), and the anemic anoxia surpasses it, all the hearts are weakened, become dilated, and develop hemic murmurs.

5. That, whenever anemia prevails in a group of patients, this special compensatory mechanism develops among them with more frequency, and, hence, with less frequency will hemic murmurs appear among them during subsequent anemias.

6. That youthfulness does not necessarily imply a better heart. The hearts of persons over 50 years of age, after having developed this special compensatory mechanism, are more efficient in withstanding anemic anoxia than the youthful hearts of persons less than 30 years of age that have not as yet developed this special compensatory mechanism.

7. That, after this special compensatory mechanism is developed, it continues to function throughout life, and allows the heart to withstand severe subsequent anemias that may develop in old age (over 50 years), and even in senility (over 70 years), without weakening, dilating, or developing hemic murmurs.

8. That, by inference, (a) since the ability of the heart to tolerate anoxia of exercise induced by increased metabolic rate, with its enormous increase in oxygen demand (it is calculated that, in spite of its small size compared with that of the rest of the body, the heart burns during exercise as much oxygen as the rest of the body during repose), is the fundamental basis of all tests for cardiac reserve; (b) since anoxia induced by exercise is even being substituted by anoxia induced by reduction in oxygen tension of the inspired air in special electrocardiographic tests of cardiac efficiency;[5-7, 12, 13] and (c) since anoxia is the fundamental factor, and it makes no difference whether myocardial anoxia is induced by anemia or by exercise; therefore, a heart compelled to develop this special compensatory mechanism for anemic

anoxia, if it continues to function throughout life, would be just as well prepared to withstand, with the same ease, the anoxia of exercise as the anoxia of future anemias; and, hence, a previous, temporary anemia may be capable of permanently transforming an ordinary, normal heart into a more efficient one with greater cardiac reserve and more functional capacity.

9. That, by inference, since, physiopathologically, it also makes no difference whether anoxia is of anemic or ischemic (obstructive) origin, the same special compensatory mechanism will enable the heart to withstand anemic as well as ischemic anoxia; and, therefore, after this special compensatory mechanism is fully developed, the heart would be just as well prepared to endure, with the same impunity, subsequent anemias that may develop in old age, as well as the coronary sclerotic changes of late middle, and old, age.

Thus we may say that the new cardiologic phenomenon, mentioned in the beginning, whose presence was suggested by clinical observations, probably exists, and does not necessarily constitute a great paradox, namely, *moderate temporary anemia may exert a beneficial effect on the heart by compelling it to develop some special compensatory mechanism that continues to function throughout life, and allows the heart to tolerate with impunity, up to a certain limit, the myocardial anoxia that develops from subsequent anemias, as well as from exertion or coronary sclerosis.*

We have to try now to find a reasonable physioanatomic explanation of the nature of this special compensatory mechanism and the manner in which it is developed.

It is known, of course, that compensation for anemia is carried out by the organism as a whole; in part, by forcing hemoglobin to liberate a greater amount of its load of oxygen to the tissues; in part, by forcing the tissues to utilize oxygen with greater efficiency; but mainly, by forcing the heart to pump an increased minute-volume of blood to the tissues.[26, 27]

Scaramucci, an Italian of the seventeenth century, first called attention to the fact that the flow of blood in the coronary arteries occurs mainly during diastole, instead of systole, as in the rest of the arterial tree, because the coronary arteries are compressed during systole by the contraction of the cardiac muscle. We also know that tachycardia takes place mainly at the expense of the diastolic period, with relatively little reduction in the systolic period. Tachycardia, therefore, results in a greater increase in transportation of oxygen throughout the systemic arterial system than in the coronary arteries.

In order that the heart may be able to compensate for its own anemic anoxia, with the added burden of the increased work that is imposed upon it to compensate for the anemic anoxia of the entire organism, and without being able to utilize as favorably its own increased rate for its own increased oxygenation, it must necessarily provide itself

with an added means of augmenting the minute-volume flow of blood that reaches its muscle fibers.

According to Wearn,[22] the adult human heart has what can be called a perfect proportion of one capillary per muscle fiber. This represents an average of approximately 3,342 capillaries per square millimeter of cardiac muscle, and about twice the number of capillaries per muscle fiber in skeletal muscles. Obviously, any compensatory increase in blood supply to the heart muscle should be looked for in the coronary arterial system that supplies this prodigious capillary bed.

It is no longer considered that the coronary circulatory system is an *end-artery* system. On page 549 of *Gray's Anatomy*, twenty-fourth edition, it is stated that there is an extensive anastomosis between the small branches of the coronary arteries in the substance of the heart. Besides these extensive intercoronary anastomoses, the coronary arteries communicate with extracardiac arteries and also with the ventricular cavities through arterioluminal and arteriosinusoidal vessels.[4, 22]

According to Goldsmith and Butler,[21] among the higher vertebrates the thebesian or intertrabecular circulation is the primitive one and the one that functions in the fetus long before the coronary system is developed. Some of these thebesian vessels become permanently incorporated in the coronary arterial system, and some remain as permanent arterial communications between the coronary arteries and the internal cavities of the heart. The thebesian veins drain the capillary spaces directly into the internal cavities of the heart. By retrograde flow these veins may also contribute to the nutrition of the myocardium.

We see, therefore, that in the anatomic sense the coronary arteries are not terminal arteries. Nevertheless, all this vast net of collateral vessels exist only as a potential, nonfunctioning, impermeable anastomosis. Hence, in the physiologic sense the coronary artery system continues to be an end-artery system, and myocardial infarction occurs when one of its branches is suddenly obliterated.[22]

Blumgart, Schlesinger, and Davis[19] have shown that in the normal heart there are no intercoronary anastomoses larger than 40 micra in diameter, but that anastomotic vessels less than 40 micra in diameter are very numerous, and that they can be easily demonstrated when injections are performed with watery fluid of low viscosity. In other words, these numerous intercoronary anastomotic vessels which are found in normal hearts are too small to permit the flow of a liquid with the viscosity of normal blood, and, therefore, are of no functional significance.

On the contrary, in hearts which were the seat of chronic coronary obstruction these authors were able to demonstrate a marked increase in the size of these intercoronary anastomotic vessels, reaching up to 200 micra in diameter, and, hence, with full functional capacity because they could be injected with a lead-agar mass. Furthermore, these authors proved by comparative clinicopathologic studies that, if

occlusion of a coronary artery takes place gradually, throughout months or years, with a concomitant efficient development of these intercoronary anastomotic vessels, (1) the supply to the corresponding portion of myocardium remains adequate for the ordinary activities of life; (2) there are no demonstrable physical signs or symptoms during the lifetime of the patient; and (3) no scar can be demonstrated in the myocardium at autopsy. Therefore, the extraordinary compensatory significance of collateral circulation through enlarged intercoronary anastomotic vessels in myocardial areas subjected to chronic ischemia is emphasized.

Now these enlarged, fully functional, intercoronary anastomotic vessels, with full compensatory capacity, have been demonstrated both at autopsy and experimentally in dogs, always and exclusively associated with chronic obstruction in the coronary arteries and their branches.[19, 20, 24] Therefore, it has been generally believed that the increase in pressure induced by chronic obstruction in the coronary circuit is the only factor responsible, and the only one able to force dilatation and to initiate blood flow, with subsequent development of these small, previously impervious and nonfunctioning intercoronary anastomotic vessels.

Anemia causes no increase in pressure in the coronary circuit, but, since anemia reduces considerably the viscosity of the blood and through anoxemia induces very marked vasodilatation, and since in circulatory dynamics the sum of these two factors, vasodilatation plus reduced viscosity, is always capable of compensating for a lack of a moderate increase in pressure, we may conclude tentatively:

1. That it is not necessary, as is generally believed, for the coronary arteries to become chronically obstructed in order to force, through an increase in pressure, these collateral intercommunicating vessels to become dilated and assume efficient function.

2. That anemia by itself, with the ordinary pressure in the coronary circuit, but helped by the vasodilatation and reduction of blood viscosity that it produces, may be equally capable of starting blood flow, with the subsequent development of the collateral anastomotic vessels of the coronary arterial system.

3. That, with chronic coronary obstruction, the increased pressure induced in the coronary circuit can only exert its force and produce active dilatation in the intercoronary communicating branches; the other, very important arterioluminal and arteriosinusoidal anastomotic vessels could not be affected directly because the flow of blood in these vessels is in an opposite direction, that is, from the ventricular cavities toward the capillary bed of the myocardium.

4. That, with anemia, on the contrary, the passive, spontaneous vasodilation induced by anemic anoxia, plus the reduced viscosity of the blood, would exert an opening effect in the entire system of previously impervious anastomotic vessels.

5. That this probable ability of anemia to establish efficient function in the whole, vast, previously impervious collateral anastomotic circulatory system of the heart, including the extracardiac, arterioluminal, and arteriosinusoidal, besides the intercoronary vessels, may account for the special compensatory mechanism that the heart is capable of developing when compelled to do so by anemic anoxia.

Furthermore, how jealously the human organism guards itself against anoxemia and the numerous defences that are capable of being called into action as soon as oxygen hunger develops are well known. Since in the anoxemia of high altitudes (over 5,000 ft.) the organism is capable of compelling the hematopoietic system to produce a compensatory hyperglobulia and hyperhemoglobinemia; since, as shown experimentally in dogs by Whipple,[24] when anemia is superimposed on a severe dietary protein restriction, the organism is capable of altering protein metabolism in order to utilize the little amount of protein ingested, first and preferably, in the manufacture of hemoglobin, before any serum albumin or serum globulin is formed, with complete disregard for the edema which results from reduced osmotic pressure in the blood; since, in anemic anoxia, as mentioned before, the organism is capable of altering the oxidative processes in order to compel the hemoglobin to liberate a larger proportion of its oxygen load to the tissues and to compel the tissues to utilize oxygen more efficiently; and since, even in avascular tissues like the cornea, when its oxidative system is impaired, compensatory vascularization takes place to overcome local asphyxia, it should also be possible and is to be expected that, in the presence of chronic myocardial anemic anoxia, the organism may simply call into rapid growth and full function its vast reserve of undeveloped collateral anastomotic coronary vessels, in order to provide the myocardium with a compensatory increase in blood supply.

This is probable, not only from a physiologic point of view, but anatomically, it is also feasible, for, according to Goldsmith and Butler,[21] the coronary arterial system probably develops by budding instead of by the coalescence of intercellular spaces; and, according to Wearn,[22] there is a *constant morphologic alteration in the coronary circulation of the normal human heart*, with progressive improvement in the capillary, muscle-fiber ratio from one capillary per five muscle fibers at birth to one capillary for each muscle fiber at full maturity (30 years of age), after which this ratio remains constant throughout life.*

Hence we venture to propose the following tentative theory:

The existence of a moderately severe but tolerable anemia for a sufficient length of time is capable of exerting a distinctly beneficial effect

*Wearn states that this increased capillary, muscle-fiber ratio does not tend to improve the nutrition of the adult cardiac muscle fiber because the adult myocardial fiber is approximately 5 times as large as those of the newborn. Thus, the higher incidence of hemic murmurs among anemic persons less than 30 years of age, as compared to those over 30 years old, as shown in Tables II and III, cannot be explained by this improved capillary, muscle-fiber ratio of adults.

on the normal human heart by permanently changing the imperfect, susceptible, and dangerous coronary circulatory system (of the end-artery type, in the physiologic sense) into a much more efficient, well-guarded, nonsusceptible, and nondangerous one, with total development and full function in all its vast reserve of intercommunicating vessels.

That nature, a priori, should not deny man a physiologic method of developing the facultative function of this vast net of collateral anastomotic vessels in order to perfect the cardiac coronary arterial system and bring it up to par with the prodigious capillary bed with which the heart is provided beforehand, should follow from the fact that there is provision for a period of physiologic anemia in infancy, during all the time of exclusive lactation beyond six months, because of the deficiency of iron in milk, and because the child can accumulate only about a six months' reserve of iron during fetal life.

And while modern pediatricians pride themselves for their efficiency in eliminating this physiologic anemia of infancy with their ever advancing methods of supplementary feedings, modern surgeons are exerting themselves in trying to develop and to perfect even the most heroic surgical methods[28-32] that would give the desperately needed additional blood supply to the hearts of an ever increasing number of middle-aged patients, especially among the intellectual classes.

According to Marvin,[33] among these surgical methods, cardio-omentopexy and the implantation of the pectoralis minor on the heart have proved so far of very limited value, and he believes that they will have to be abandoned, but Brauer's artificial adhesive mediastinopericarditis has helped a few patients, and cannot be totally discarded.

May the day come soon when we can identify beyond doubt, and can feel fully justified in cooperating with, nature's methods, and can discard all heroic surgical procedures, not because of their imperfections, but because they are not necessary.

White, at the end of his book on heart disease,[3] has added an appendix of cardiological questions that have not been answered. Number 105, on page 885, reads as follows: *"Why is angina pectoris so rare in the Negro race"?* This is so, in spite of the fact that syphilis is more prevalent among Negroes than among whites in America. Among these American Negroes there are also much poverty, avitaminosis, and protein malnutrition, besides uncinariasis (in the South) and the habit of prolonged breast feeding of their children. Anemia in their youth, therefore, may have improved their coronary circulatory system to such an extent that, when they reach late middle age, they are capable, as are the peasants (whites) in Puerto Rico, of enduring aortitis and coronary artery disease without developing cardiac anoxia, and, hence, without angina pectoris.

Naturally, our only intention has been to try to develop and to propose this tentative theory, and not to commit the error of assuming that it is already established and could have any application as yet.

We do not call this a preliminary report only because we are afraid that, in the mountains of Puerto Rico, without facilities, we shall never be able to proceed any further, but we ardently hope that someone better equipped will be sufficiently stimulated to carry on and see whether it is possible to demonstrate, experimentally in dogs kept sufficiently anemic for a sufficient length of time, and in autopsies in cases in which there was a definite history of anemia in youth, the presence of a structural improvement in the coronary circulatory system.

Substantiation of this theory, and not its enunciation, would represent a truly valuable contribution to humanity, for only its absolute verification would make its application permissible, and only then would a promising new road be laid open to the prophylaxis of coronary heart disease, and, perhaps, even to the addition of a number of useful years to the average life span of man.

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CARDIAC HYPERTROPHY OF UNKNOWN CAUSE

A Study of the Clinical and Pathologic Features in Ten Adults

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THERE is a group of cases, observed in youth and in adult life, which is characterized chiefly by cardiac hypertrophy of obscure etiology. Most of these patients suffer, over varying periods of time, from recurring attacks of cardiac insufficiency of increasing severity; some die suddenly. Excluding the ten cases forming the basis of this study, reports of only fourteen examples of this condition were found in which a careful search at autopsy failed to reveal lesions characteristic of the familiar causes of heart disease. The first was recorded by Josserand and Gallavardin,[1] in 1901 (their Case 3). Laubry and Walser[2] reported a second in 1925, and applied the descriptive term "myocardie." Walser,[3] in his monograph, added a third. Cabot's messenger boy[4] first had symptoms of heart failure one year before his death at the age of 16 years. In 1933, Levy and Rousselot[5] reported three cases in young adults, one of which was subsequently discarded because of the possibility that the cardiac lesions were due to abnormal glycogen storage (von Gierke's disease). Whittle's Cambridge student,[6] referred to by these authors, should likewise be omitted, for post-mortem examination revealed a hypoplastic aorta and an enlarged thymus gland.

In 1937, Levy and Von Glahn,[7] in abstract form, recorded observations on ten cases, including two of those previously reported by Levy and Rousselot. It became apparent that, although the condition was uncommon, it was not as rare as had been believed, and that it presented a distinct pattern, both clinically and at autopsy. Subsequently, von Bonstorff[8] described eight cases from the Thorndike Memorial Laboratory of the Boston City Hospital, and Reisinger and Blumenthal,[9] two cases from the Veterans' Administration in Washington. Three additional cases included by the latter authors are not considered acceptable because of probable syphilitic lesions in the aorta. The tobacconist, whose story was given by Kjaergaard[10] and cited by von Bonstorff, must be omitted because of the incomplete autopsy notes and the statement that, microscopically, fatty degeneration and slight inflammatory lesions were found in the heart. Eleven cases are mentioned as falling into the category of "hypertrophy of uncertain

etiology" by Kaplan, Clark, and de la Chapelle,[11] and another is referred to by Dexter and Farnsworth,[12] but individual histories and autopsy protocols are lacking, so that they cannot properly be included in the series. Deficiency of vitamin B was considered responsible for the cardiac disturbances in Dock's cases.[13] Those of Smith and Furth[14] were characterized by marked and widespread endocardial fibrosis. There is a curious form of degeneration of the myocardium associated with pregnancy and the puerperium, which results in congestive heart failure.[15, 16] It presents the common factor of unknown cause, but does not otherwise resemble the disorder with which we are concerned.

Although the main features of the ten cases to be described were given in our preliminary paper,[7] it has seemed desirable to document them by clinical histories and autopsy notes, as well as by suitable illustrations. A collection of such studies eventually may give a clue to the etiology.

ABSTRACTS OF CLINICAL RECORDS AND AUTOPSY PROTOCOLS

CASE 1.*—Unit No. 81203. G. T., a Negro man, married, aged 31 years, was admitted to the surgical service on May 10, 1929. He had been a rock-driller for ten years. He complained of a painful swelling in the right groin which had been present for three weeks. There were no cardiac symptoms. He gave an indefinite history of "rheumatism" in the right hip fourteen years previously, which never recurred. He had gonorrhea at the age of 14 years. He never had a serious illness. He smoked two packages of cigarettes a day and rarely took alcohol.

Examination showed that the heart was enlarged to the left. The sounds were of poor quality, and a soft systolic murmur was heard at the apex. The blood pressure was 100/60. The Wassermann reaction of the blood was negative. The leucocyte count was 9,700, with 70 per cent polymorphonuclears. The urine contained neither albumin nor sugar. Roentgenograms of the chest showed no areas suggesting tuberculous infiltration, but the heart shadow was enormously enlarged, particularly to the left.

A mass of infected lymph nodes in the right inguinal region was incised and drained. Microscopic examination of a bit of tissue removed at operation showed no tubercles and no caseation necrosis. A definite diagnosis of tuberculous adenitis could not be made. The patient was discharged on May 19, with a granulating wound.

Two weeks later he entered the city tuberculosis sanatorium at Seaview, where he remained two and one-half months. While there, an inguinal hernia was repaired. He gained 10 pounds and was told that he did not have pulmonary tuberculosis. The night before he left this institution he had his first attack of dyspnea, and was unable to sleep because of difficulty in breathing. In spite of this fact, he soon returned to his job, but after working for one day he again had a sudden attack of shortness of breath, and was obliged to stop. Dyspnea continued, and palpitation and precordial pain appeared. On September

*Cases 1 and 7 were described in a previous paper (Levy and Rousselot,[5] Cases 1 and 3). In order to bring all of the material together, they are reported again.

2 (three and one-half months after leaving the hospital and three days after resuming work), he was readmitted to a ward of the Presbyterian Hospital.

On admission, he was quite short of breath and looked ill. The temperature was 101.2° F. There were coarse râles scattered throughout both lungs. The heart was greatly enlarged to the left. The rate was 104, the rhythm was regular, and the sounds were of fair quality. There was a soft systolic murmur at the apex. The blood pressure was 98/72; it rose on the following day to 106/86. There was slight clubbing of the fingers. The liver and spleen were not enlarged. The erythrocyte count was 4,260,000; the hemoglobin, 80 per cent; and the leucocytes, 7,800, with 64 per cent polymorphonuclears. The Wassermann reaction of the blood was again negative. No tubercle bacilli were found in the sputum at any time. The blood urea was 26 mg. per 100 cubic centimeters. Numerous blood cultures were negative. Roentgenograms of the chest showed patchy areas of density in the lower third of the right lung, suggesting pneumonic consolidation. The heart shadow was enormously enlarged. The electrocardiogram showed sinus tachycardia, with a rate of 120, and well-marked left axis deviation. The P-R interval was 0.15 second. The T wave was inverted in Leads I and II, and upright in Lead III.

There was continuous elevation of temperature, with fluctuations from 98 to 104.8° F. There was also sustained tachycardia; the rate usually ranged between 90 and 110. On November 14, auricular fibrillation, with a rate of 72, was observed. Four days later, sinus rhythm reappeared. The leucocytes were never greatly increased; the highest count recorded was 12,000, with 85 per cent polymorphonuclears. There was no anemia.

On September 12 (ten days after admission) he complained of sudden blindness in the left eye, and it was apparent that an embolus had lodged in the central artery of the retina. Subsequently, expectoration of blood and pain in the left lumbar region suggested infarction of the lungs and left kidney. The blood pressure remained low—100 to 108 mm. Hg. systolic; 64 to 88, diastolic. Cardiac insufficiency gradually increased and a cardiac psychosis developed. He died on December 30 (four months after admission), of advanced myocardial insufficiency.

Clinical Diagnosis.[*]—Cardiac hypertrophy; cardiac thrombosis; chronic myocarditis; infarcts of lung and spleen; embolism of central artery of retina.

Autopsy No. 10368.—Heart: Weight, 640 grams. There were small deposits of fibrin on the pericardial surface of both auricles and each ventricle; these were most marked at the apex. The auricles were of normal size, the ventricles were dilated, especially the right ventricle in the region of the conus. Both ventricular walls were hypertrophied; the right measured 1.1 cm., the left, 2.5 cm., in thickness. The papillary muscles of the right ventricle were somewhat hypertrophied. At the apex of the right ventricle there were numerous small thrombi, and similar thrombi were present between the columnae carneae at the apex of the left ventricle. Beneath these thrombi in the left ventricle the myocardium was greatly thinned out, and fine fibrous strands extended from the endocardium into the muscle. The endocardium of the septal portions and anterior wall of the right ventricle was thick-

ened to form narrow white streaks. The endocardium of the left ventricle was thickened. The tricuspid valve had four cusps; the other valves were normal except for slight thickening of the margin of the mitral cusps.

The coronary arteries were normal except for slight intimal thickening of the left branch.

Aorta: Normal.

Histologic Examination.—The myocardium was hypertrophied; the nuclei were irregular in shape. Occasionally, small hemorrhages separated the muscle fibers. On the endocardial surface there were completely organized and more recently formed thrombi. There was no acute inflammatory reaction. Gram and Levaditi stains did not reveal any organisms.

Final Note.—The central lesion at autopsy was an enlarged heart, with parietal thrombi but without any significant valvular or myocardial lesions. The changes in the other organs were those associated with embolism and infarction from mural thrombi and with cardiac insufficiency. It view of the patient's history of ten years of rock-drilling, one might anticipate silicotic changes. The cough and roentgenologic observations were in accord with this possibility, but sections of the lung offered no support for this diagnosis. The enlarged lymph nodes in the groin, because of which the patient originally entered the hospital, contained structures which resembled tubercles, but the etiology could not be proved. The cause of the cardiac dilatation and mural thrombosis remained undiscovered. There were no clear-cut inflammatory changes other than those associated with the organizing thrombi.

Anatomic Diagnosis.—Cardiac hypertrophy and dilatation; mural thrombi in ventricles; infarcts of lung, right, and both kidneys; chronic passive congestion of viscera; hydrothorax, bilateral; hydropericardium; ascites; edema of extremities; tuberculosis of inguinal lymph nodes; chronic prostatitis; congenital malformation of heart (patent foramen ovale and quadricuspid tricuspid valve).

CASE 2.—Unit No. 52367. E. H., a white woman, aged 48 years, a housewife, was admitted to the hospital on Dec. 23, 1921, complaining of shortness of breath and pain in the lower abdomen. Several years previously hysterectomy was performed because of bleeding fibroids. For eight months she was short of breath and distended. There was pain in both arms and in both lower abdominal quadrants. The ankles and legs were swollen for two months.

Examination showed dyspnea, orthopnea, and cyanosis. The veins of the neck were distended. The temperature was 100.4° F. There were signs of congestion in both lungs, with fluid in the right pleural sac. The heart was greatly enlarged to the left. The cardiac rhythm was totally irregular; the rate ranged from 80 to 120. The blood pressure was 130/80. The liver was enlarged. There was marked edema of the lower extremities.

During the night after admission she became weaker, the pulse grew feebler, and she died of myocardial insufficiency.

Clinical Diagnosis.—Chronic myocarditis; cardiac hypertrophy and dilatation; cardiac insufficiency; auricular fibrillation.

Autopsy No. 9185.—Heart: Weight, 550 grams. There was an adhesion between the posterior surface of both ventricles and the parietal pericardium; this adhesion covered an area of about 4 cm., with its

upper margin at the auriculoventricular grooves. The apex of the heart was blunt and rounded, and was formed by both ventricles. All of the cavities were dilated, especially that of the right ventricle. The various valves were normal. At the apex of the left ventricle there was a large, dark-red thrombus with a corrugated surface. The endocardium of the left ventricle was grey and more opaque than normal, but in the other chambers it was unaltered. The myocardium was pale red, flabby, and without any obvious increase of connective tissue. The right ventricle was 6 mm. in thickness, the left, 14 millimeters. Only a few areas of early sclerosis were found in the coronary arteries.

Aorta. This was moderately sclerotic.

Histologic Examination.—Heart: The myocardium of the left ventricle was moderately hypertrophied; the nuclei were larger than normal and were hyperchromatic. There was no necrosis and no scarring. The capillaries were engorged (Fig. 1). The arterioles were normal.
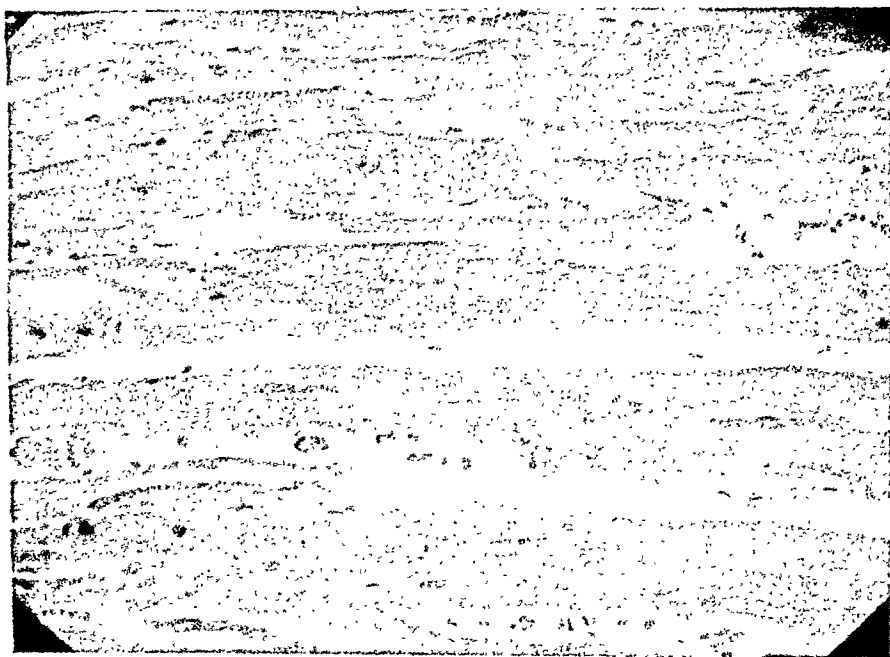
Fig. 1.—Case 2. Hypertrophy of myocardium.

Final Note.—The autopsy offered no satisfactory explanation of the cardiac derangement. There were no changes in the myocardium or peripheral arteries sufficient to explain the cardiac incompetency.

Anatomic Diagnosis.—Cardiac hypertrophy; pericardial adhesion; thrombus of left ventricle; infarcts in lung, right, and kidney, left; chronic passive congestion of viscera; hydrothorax, right; ascites; adenoma of thyroid.

CASE 3.—Unit No. 356074. D. E., a white man, aged 56 years, married, an unemployed salesman, was admitted to the hospital on Oct. 7, 1932, complaining of swelling of the ankles and asthma. He had pneumonia twelve years previously, and this was followed by attacks of asthma, which persisted. There was almost continuous wheezing; dyspnea was worse on exertion. Skin tests were negative for allergic sensitivity. The asthma was worse in winter than in summer. Eating beef and exposure to dog's hair aggravated the condition.

Three months earlier his business failed and he was forced to give up his motor car. This necessitated more walking, and he climbed many flights of stairs in the effort to make a living. Edema of the ankles steadily increased. He was given digitalis without apparent benefit. For twenty-four hours before admission, his wife noted cyanosis and an increase in the heart rate to 120.

Examination showed the man to be acutely ill, cyanotic, dyspneic, and orthopneic. There were râles and dullness at the bases of both lungs. The heart was greatly enlarged. The rate was 100; the rhythm was regular save for occasional premature beats. The sounds were feeble; a blowing systolic murmur was heard at the apex. The blood pressure was 150/95. The liver was enlarged. There was marked edema of the extremities. The peripheral arteries were thickened.

The temperature was normal. The leucocytes numbered 13,200, with 73 per cent polymorphonuclears. The Wassermann reaction of the blood was negative. The blood urea was 41 mg. per 100 cubic centimeters. A roentgenogram of the heart showed the total transverse diameter to measure 14.2 cm.; the internal diameter of the chest was 26 centimeters.

The following morning he was less cyanotic, but the respirations were shallow. The blood pressure fell to 115/75. He was placed in an oxygen tent and was given digitalis. He died twenty-three hours following admission, after expectorating a mouthful of dark blood.

Clinical Diagnosis.—Interstitial emphysema, postinfectional; chronic bronchitis; myocardial disease due to emphysema; arteriosclerosis of coronary arteries; cardiac insufficiency.

Autopsy No. 11063.—Heart: Weight, 480 grams. Along the auriculo-ventricular grooves there was a considerable amount of fat. The pericardial surfaces were smooth. The cavity of the right ventricle was slightly enlarged; the ventricular wall was 7 mm. in thickness. The wall of the left ventricle was 20 mm. thick; the cavity of the ventricle was only a little larger than normal. The myocardium was dark-red, coarser than normal, and did not appear scarred. There was moderate hypertrophy of the papillary muscles of the left ventricle. The leaflets of the aortic valves were somewhat thickened in their basal portions, whereas the other parts of the cusps were thin and delicate. The other valves were normal. In the intima of the coronary arteries there were small yellow plaques that were not calcified and did not narrow the lumen.

Aorta: A few scattered yellow areas were seen in the intima of the ascending portion of the vessel. Similar areas were more numerous in the thoracic and abdominal portions; in the latter situation some of the plaques had undergone fatty degeneration, but none was calcified.

Histologic Examination.—Heart: The muscle fibres were larger than normal, their nuclei hyperchromatic and of irregular shapes. The myofibrils were coarse. The muscle coat of the arterioles was somewhat hypertrophied. The veins were distended.

Aorta: The section included one of the largest plaques. The changes were those of moderately advanced sclerosis.

Final Note.—There were no cardiac lesions of any importance. The remaining visceral lesions were trivial, and threw no light on the case.

Anatomic Diagnosis.—Cardiac hypertrophy and dilatation; edema of legs and back; chronic bronchitis; benign hypertrophy of prostate; arteriosclerosis, mild.

CASE 4.—Unit No. 282949.   J. R., a Negro man, aged 42 years, single, an elevator operator, was first admitted to the hospital on Jan. 9, 1931, complaining of pain in the abdomen and swelling of the testicles.   He had typhoid fever at 12, and pneumonia at 30 years.   There were frequent attacks of tonsillitis up to 1921, but none thereafter.   He had a chancre when a young man, which was cauterized.   He received no other treatment; no other symptoms of syphilis developed.   He took one or two drinks of whiskey and smoked fifteen to twenty cigarettes daily.   He passed a lodge examination three years earlier.

Ten days previously he noted shortness of breath after mounting two or three flights of stairs.   There was also severe pain in the right upper abdominal quadrant, followed, a few days later, by swelling of the scrotum.

Examination showed dyspnea but no orthopnea.   The retinal arteries were slightly sclerosed.   There were râles at both lung bases.   The heart was enlarged.   The sounds were faint, with tick-tack quality.   The blood pressure was 170/110.   The liver was enlarged.   There was marked edema of the legs, sacral region, penis, and scrotum.

The Wassermann reaction of the blood, repeated on three occasions, was negative.   The spinal fluid Wassermann was likewise negative. There was slight secondary anemia.   The leucocytes numbered 10,500, with 65 per cent polymorphonuclears.   The blood urea was 21 mg. per 100 cubic centimeters.   The electrocardiogram showed regular sinus rhythm; T_1 and T_2 were upright, and T_3 was inverted (Fig. 2).   A roentgenogram of the heart showed the transverse diameter to measure 15 cm.; internal diameter of the chest was 25.5 centimeters.   The aorta was dilated, particularly in its ascending portion, suggesting aortitis. There were slight fever, up to 99.8° F., and moderate tachycardia; both subsided.   Four days after admission the blood pressure was 126/82; subsequently it fell to 115/70.

There was marked improvement following the usual therapy for cardiac insufficiency, and he was discharged at the end of three weeks.

He did not report until Nov. 3, 1933, and gave only a brief account of himself during the interval of nearly three years.   He remained up and about.   There were almost constant edema and some dyspnea.   For four days the symptoms had been markedly accentuated.

Examination was essentially as previously described.   The blood pressure was 120/90.   There was ascites, as well as edema of the extremities, sacral region, and scrotum.   The leucocytes numbered 9,900, with 64 per cent polymorphonuclears.   The Wassermann reaction of the blood was again negative.   The electrocardiogram was similar to the one taken in 1931.   There was no fever.

The patient died suddenly twenty-four hours after admission, with marked dyspnea but no cardiac pain.

Clinical Diagnosis.—Generalized arteriosclerosis; arteriosclerotic heart disease; cardiac hypertrophy due to overstrain; cardiac insufficiency.

Autopsy No. 11373.—Heart: Weight, 500 grams.   It was symmetrically hypertrophied.   A few grey, nodular thickenings of the epicardium were seen along the branches of the right coronary artery.   The epicardium elsewhere was normal, and the subepicardial fat was abundant. The wall of the right auricle was thicker than normal.   The tricuspid leaflets were edematous along the free margins.   The chordae tendineae were delicate.   The cavity of the right ventricle was enlarged.   The left auricle was not dilated.   Along the line of closure of the anterior cusp

of the mitral valve there was a row of minute, greyish-yellow nodules. The chordae tendineae were normal. The papillary muscles were large, and, beneath the endocardium of the anterior muscle, there was a small, recent hemorrhage. The pulmonic and aortic valves were normal. The endocardium throughout the heart was normal. The myocardium was firm, reddish brown, and somewhat coarsely trabeculated. No scarring could be seen. The wall of the right ventricle measured from 3 to 5 mm. in thickness, and that of the left ventricle, 15 millimeters. Only an occasional, small, sclerotic plaque was found in the intima of the proximal portion of each coronary artery.

Aorta: A few atherosclerotic plaques were present.
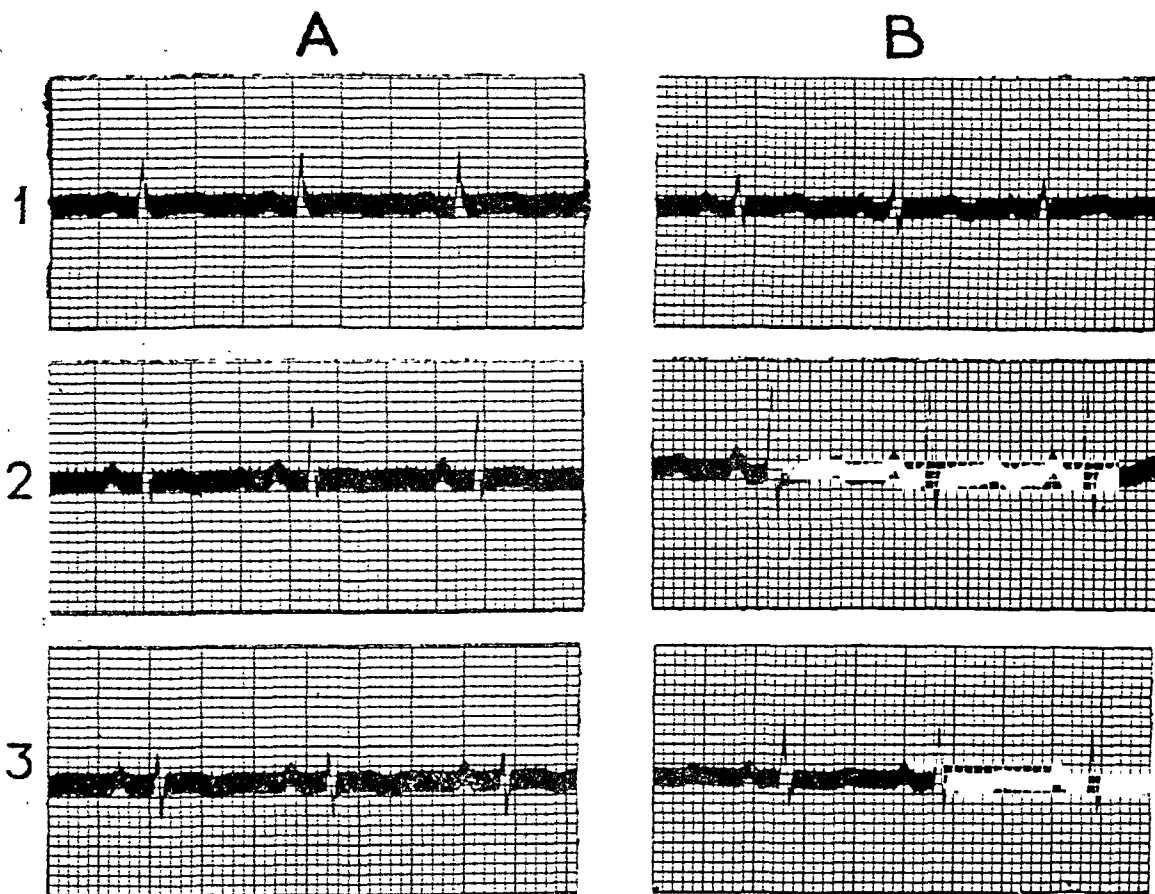
Fig. 2.—Electrocardiograms in Case 4. *A*, Jan. 10, 1931; sinus rhythm; rate 98. P-R = 0.16 second. T waves are of low amplitude in Lead I; inverted in Leads II and III. Patient received 0.9 Gm. of digitalis on preceding day. *B*, Nov. 4, 1933; slight alterations in T waves, due probably to absence of digitalis effect. No changes indicating serious myocardial damage. Patient died suddenly ten hours after this record was taken.

Histologic Examination.—Heart: The myocardium was hypertrophied, and the nuclei were hyperchromatic. There was no scarring. The intima of an occasional small branch of the coronary arteries was slightly thickened, whereas that of a larger branch was moderately thick, but the lumen was very little reduced in size and the heart muscle supplied by it was intact. Section through one of the nodules on the mitral valve did not disclose any evidence of rheumatic disease.

Aorta: The intima was uniformly and moderately thickened by fibrillar material. The media and adventitia were normal.

Final Note.—No explanation was forthcoming for the very decided cardiac hypertrophy, especially of the right ventricle. There was only one blood pressure reading; it indicated hypertension two years before,

but the recent measurements had been low. Aside from the lack of positive data, no arteriolar lesions of any significance were found to support a diagnosis of hypertensive disease.

Anatomic Diagnosis.—Cardiac hypertrophy and dilatation; chronic passive congestion of viscera; edema of lungs; anasarca; ascites; ulcer of stomach, healed.

CASE 5.—Unit No. 34039. H. S., a white man, aged 67 years, single, a porter, was first admitted to the hospital on Feb. 15, 1917, complaining of dyspnea. He was born in Germany and worked there on a farm. At 27 years, he had smallpox. For six years he worked around the Presbyterian Hospital as porter and handy man. He took two beers daily and a drink of whiskey before breakfast, as well as an occasional glass of wine. He smoked two pipes a day and an occasional cigar.

For one month he had noted difficulty in breathing on climbing stairs. This became progressively more marked and work was impossible. Soon after dyspnea appeared, his feet began to swell. There was no cardiac pain.

Examination showed moderate dyspnea. The lungs were normal. The heart was markedly enlarged. The sounds were faint. The rhythm was regular. No murmurs were heard. There was slight edema of the legs and feet.

The temperature rose to 100.4° F. on the second day, but returned promptly to normal. The blood pressure was 150/92. There was no anemia. The leucocytes numbered 6,500, with 74 per cent polymorphonuclears.

After six days he was discharged, improved. He worked around the hospital for two and one-half weeks and was then again admitted with the same complaints and similar findings. He improved after a rest of ten days.

His final admission was on March 29. During the eight days after his discharge he remained quiet, but dyspnea and edema recurred. A liter of fluid was removed from the right pleural cavity and 500 c.c. from the left. Gallop rhythm appeared. The temperature rose to 102.4° F. The blood pressure was 132/96. He failed to improve, and died, ten days after admission, of progressive myocardial insufficiency.

Clinical Diagnosis.—Chronic myocarditis; chronic bronchitis; cardiac insufficiency.

Autopsy No. 8704.—Heart: Weight, 620 grams. The epicardium was thickened and white over a large area on the right ventricle. In the right auricular appendage there were some small thrombi. The endocardium of all the chambers was normal. The tricuspid and pulmonary valves were normal. The mitral leaflets were somewhat thickened along the free border; the aortic cusps were moderately sclerotic at their bases, although the upper portions were thin and delicate. At the apex of the left ventricle and over the septum there were several large thrombi; the largest of these was almost 1 cm. in its greatest diameter. The endocardium beneath these thrombi was not thickened. The myocardium was coarse; its color and texture were normal, and there was no evident scarring. The right ventricular wall measured 2 to 4 mm. in thickness; the left, 14 to 16 millimeters. The coronary arteries were slightly tortuous and were almost free of atheroma.

Aorta: Above the sinuses of Valsalva there were a few small sclerotic plaques.

Histologic Examination.—Heart: The muscle fibers were hypertrophied; the nuclei were larger than normal, of irregular shapes, and

frequently hyperchromatic. In a few very small areas there was a trifling increase of connective tissue between the myocardial fibers. A section through the tip of one of the papillary muscles of the left ventricle disclosed some scarring of the myocardium, with pigment-containing phagocytes in the scar. The muscle adjacent to the scar was vacuolated. The thrombi in the left ventricle were, in part, of very recent formation, but in other portions they were older, and showed beginning organization. The endocardium and myocardium were unaltered beneath the thrombi except for those changes incident to their organization.

Aorta: The intima was slightly thickened by fibrillar tissue; the media and adventitia were normal.

Anatomic Diagnosis.—Cardiac hypertrophy; thrombi in auricle, right, and ventricle, left; infarcts of lung and kidney; chronic passive congestion of viscera; hydrothorax, bilateral; edema of lungs; benign hypertrophy of prostate.

CASE 6.—Unit No. 59224. W. J., a white man, aged 53 years, married, a dock laborer, was admitted to the hospital on Feb. 16, 1924, complaining of swelling of the legs and abdomen. He had pneumonia at 15 years of age. For about fifteen years he suffered from attacks of asthma, chiefly at night, and worse during hot weather. Asthma powders afforded relief. There was no history of venereal disease. He took an occasional drink, but never imbibed excessively. For eight or ten years he had been short of breath on climbing stairs. He worked up to the onset of the present illness.
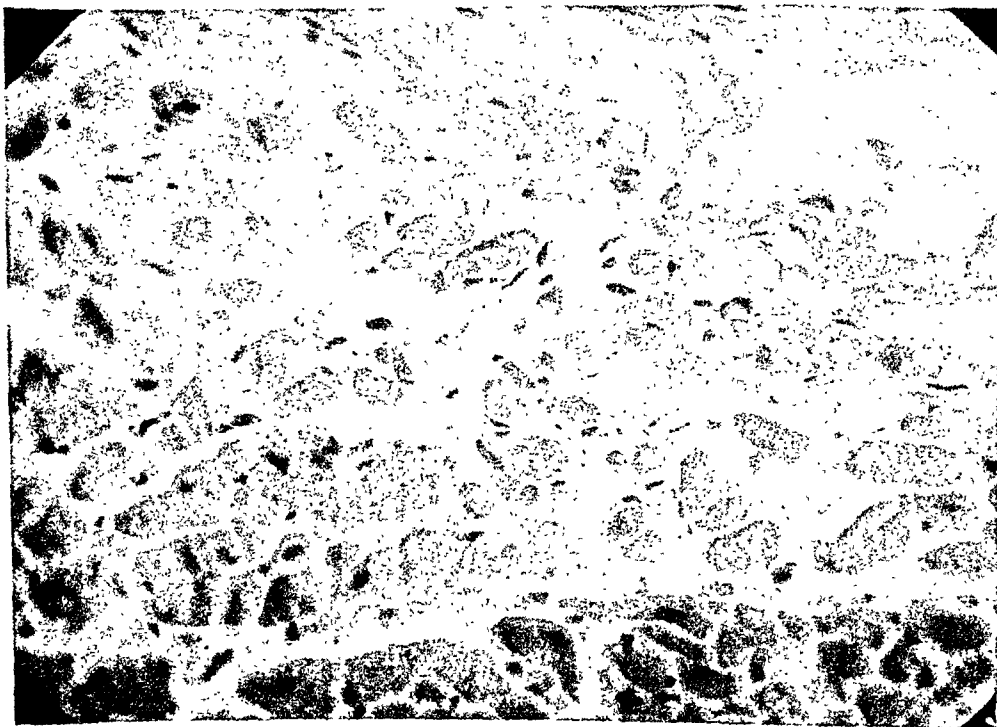
Fig. 3.—Case 6. Hypertrophy of myocardium with slight fibrosis.

Eight weeks before, he had a sharp pain in the right lower portion of the abdomen, relieved by heat. His abdomen soon began to swell, and dyspnea became so severe that he was obliged to sleep in a chair. Five days before admission his feet and legs became swollen; the swelling increased rapidly. Asthmatic paroxysms were accompanied by

pain in the region of the sternum and precordium. Attacks of cough and dyspnea caused palpitation.

Examination showed dyspnea, orthopnea, cyanosis, and marked edema of the legs, sacral region, genitals, and abdomen. Ascites was present. The heart was greatly enlarged. The rhythm was irregular; the rate, 120. The sounds were of poor quality and a loud gallop was heard. There were no murmurs. There were a few râles at the bases of the lungs. There was no peripheral vascular sclerosis. The blood pressure ranged from 110 to 150 mm. Hg, systolic, and 70 to 90, diastolic.

The temperature was 101° F. on admission, and ranged thereafter from 99 to 101.2°. A roentgenogram of the heart showed the transverse diameter to measure 17.6 cm.; the internal diameter of the chest was 31 centimeters. There was some widening of the aortic shadow. The electrocardiogram showed auricular fibrillation, with occasional ventricular ectopic beats. The T wave was inverted in Leads I and II, and upright in Lead III. Left axis deviation was present.

After rest and digitalis therapy, the heart rate fell to between 50 and 60, and there was clinical improvement. On the second day after admission, while sitting in a chair, he suddenly became dyspneic and cyanotic, and died quickly, without evidence of pain.

Clinical Diagnosis.—Chronic myocarditis; cardiac hypertrophy; auricular fibrillation; cardiac insufficiency; thrombosis of coronary artery.

Autopsy No. 9193.—Heart: Weight, 600 grams. Several small areas of thickening were present in the epicardium of the left ventricle. The mitral and aortic valve leaflets were slightly thickened, although not incompetent; the tricuspid and pulmonic valves were normal. The chordae tendineae were unaltered. The wall of the left ventricle was thickened. In the coronary arteries there were a few sclerotic plaques.

Aorta: Many large and small, elevated, yellowish-white areas were present in the intima.

Histologic Examination.—Heart: The myocardial fibers were larger than normal; the nuclei were of irregular shapes, large and hyperchromatic. Only rarely was any scarring found; this was insignificant and consisted of an increase of collagen between the muscle (Fig. 3). An occasional arteriole showed moderate eccentric thickening of its intima by fibrillar tissue. A small, fresh, endocardial hemorrhage was present in the left ventricle.

Aorta: The intima was thicker than normal, and fat-containing phagocytes, in moderate numbers, were seen in it. The media and adventitia were unaltered.

Final Note.—The pathologic study offered no explanation for the sudden death.

Anatomic Diagnosis.—Arteriosclerosis; cardiac hypertrophy; emphysema, mild.

CASE 7.—Unit No. 69800. S. R., a white man, aged 29 years, married, was first admitted to the hospital on Sept. 17, 1927, complaining of palpitation. He had been an automobile mechanic for twelve years and enjoyed unusually good health. He had gonorrhea at 20 years of age, but denied syphilis. His consumption of alcohol and tobacco was very moderate.

He first was conscious of cardiac irregularity five years previously, while working in South America. The irregular and rapid beating of his heart occurred in paroxysms lasting from five to fifteen minutes.

The attacks increased in frequency, and for two and one-half months tachycardia had persisted almost continuously.

Examination showed a large, well-developed man. There was no dyspnea or cyanosis. The lungs were normal. The heart was considerably enlarged. The rate was variable, at times 120 to 160 per minute, with regular rhythm, then a few irregular beats, followed by a sudden drop to 60. The sounds were of moderate intensity. There was splitting of the first sound at the apex. No murmurs were heard. The peripheral vessels were not thickened. The blood pressure was 110/80. The liver was not enlarged. There was no clubbing of the fingers. No edema was present.

The temperature was normal and remained so throughout his stay in the hospital. The leucocytes numbered 12,000, with 63 per cent polymorphonuclears. There was no anemia. The Wassermann reaction of the blood was negative. The urine contained a faint trace of albumin. The total transverse diameter of the heart measured 17.8 cm., the great vessels, 6 cm., and the internal diameter of the chest, 30.5 centimeters.

The heart rate varied greatly from day to day and from hour to hour. The dominant rhythm was a tachycardia which had its origin in the junctional tissues, with a rate of 50 to 160. Numerous ventricular premature beats occurred. The P-R interval, when it could be measured, varied from 0.22 to 0.31 second, and there was widening of QRS when nodal rhythm, with a slow rate, was present. The T wave was inverted in Lead I and upright in Leads II and III.

The administration of quinidine, by mouth, did not affect either the rate or the rhythm. The use of digitalis, first in full doses, and then in maintenance ration, slowed the rate to 60, with occasional short paroxysms of tachycardia during which the rate rose to 120. The blood pressure rose to 130/70. On discharge, after four weeks in the hospital, the patient felt greatly improved, and was instructed to continue with small, daily doses of digitalis.

He was lost sight of until eight months later, when he came to the clinic desperately ill. After discharge from the hospital he again went to South America on a job, but had to quit work after five weeks because of recurrence of the paroxysms of tachycardia. He returned to this country two weeks before admission, and since that time had had great difficulty in getting his breath.

On the second admission, June 4, 1928, he was cold, and a clammy sweat covered the skin. The respirations were rapid and shallow. The pulse was barely palpable. The heart rate was about 180, and the rhythm was apparently regular. The temperature was 99.4° F. The blood pressure was 134/90. The Wassermann reaction of the blood was again negative. A blood culture showed no growth. The leucocyte count was 13,000, with 42 per cent polymorphonuclears. There was no anemia. The blood urea was 41 mg. per 100 cubic centimeters. Electrocardiograms showed, at times, auricular tachycardia with a rate of 170 and incomplete bundle branch block, and, at other times, A-V nodal rhythm with a rate of 70 to 80, with complete bundle branch block and numerous ventricular premature beats. When the rate was slow, QRS measured 0.17 second; R was notched and T was inverted in all leads. The records were very different in form from those previously obtained.

Dyspnea persisted and was more marked during the paroxysms of tachycardia. The administration of large doses of digitalis was with-

out apparent benefit. He began spitting up blood, evidently as a result of pulmonary infarction. The temperature rose to 103.4° F., and the leucocyte count to 31,000, with 79 per cent polymorphonuclears. Orthopnea and prostration became extreme, and he died on June 10, six days after entering the hospital.

Clinical Diagnosis.—Cardiac hypertrophy; chronic cardiac dilatation; infarct of heart; cardiac insufficiency; paroxysmal tachycardia; infarct of lung; premature contractions, auricular and ventricular; trypanosomiasis?

Autopsy No. 10017.—Heart: Weight, 740 grams. The chambers of the heart were greatly dilated. There was hypertrophy of the columnae carneae and papillary muscles of each ventricle. At the apex of the left ventricle the wall was thin; elsewhere it was hypertrophied, as was that of the right. The right ventricle measured 0.6 cm. in thickness, and the left ventricle, 2.4 cm., except at the apex, where it was 0.5 centimeters. The only scarring found was in the posterior papillary muscle of the left ventricle. Between the columnae carneae of the left ventricle there were several small thrombi. The valves were essentially normal. The chordae tendineae were unaltered. In the anterior descending branch of the left coronary artery there were many small areas of sclerosis; the coronary arteries were otherwise normal.

Aorta: Normal except for small sclerotic areas near the origin of the branches.

Histologic Examination.—Heart: The myocardium was hypertrophied. Areas of necrosis were present. In some places the muscle was degenerating; in other portions it had been replaced by connective tissue. A dense band of fibrous tissue was found in the myocardium of the septum just beneath the endothelium; it was infiltrated with mononuclear cells. In some places the endocardial surface was covered with small thrombi.

Final Note.—Cardiac hypertrophy and dilatation were the dominant features of the post-mortem examination. There were no inflammatory or degenerative lesions in any part of the cardiovascular system. The various embolic phenomena were secondary to the cardiac thrombi. After careful study of all of the material, no etiological basis for the heart lesion could be found.

Anatomic Diagnosis.—Cardiac hypertrophy and dilatation; infarcts of heart, old and recent; fibrous thickening of endocardium of ventricle, left; thrombi in ventricle, left; infarcts of lungs; infarct of kidney, right; hydrothorax, right; edema of lower extremities; chronic passive congestion of viscera; congenital malformation of aorta (common origin of innominate and left common carotid arteries).

CASE 8.—Unit No. 497583. F. L., a white woman, aged 66 years, a housewife, was admitted to the hospital on Sept. 5, 1936, complaining of dyspnea and "heart attacks." She was never strong. She had diphtheria at 7 years of age and pneumonia at 20 and 21 years of age. She was said to have had tuberculosis at 23 years, cured after a year spent in India. Perineorrhaphy was performed at 38, and again at 41, years. Several bones had been broken in a motor car accident ten years before. She neither drank alcohol nor used tobacco.

After the attack of diphtheria at 7 years, she had generalized dropsy which confined her to bed for a year. No information concerning the heart or kidneys was available. Thereafter, she was considered well, but not robust. She always became easily winded on
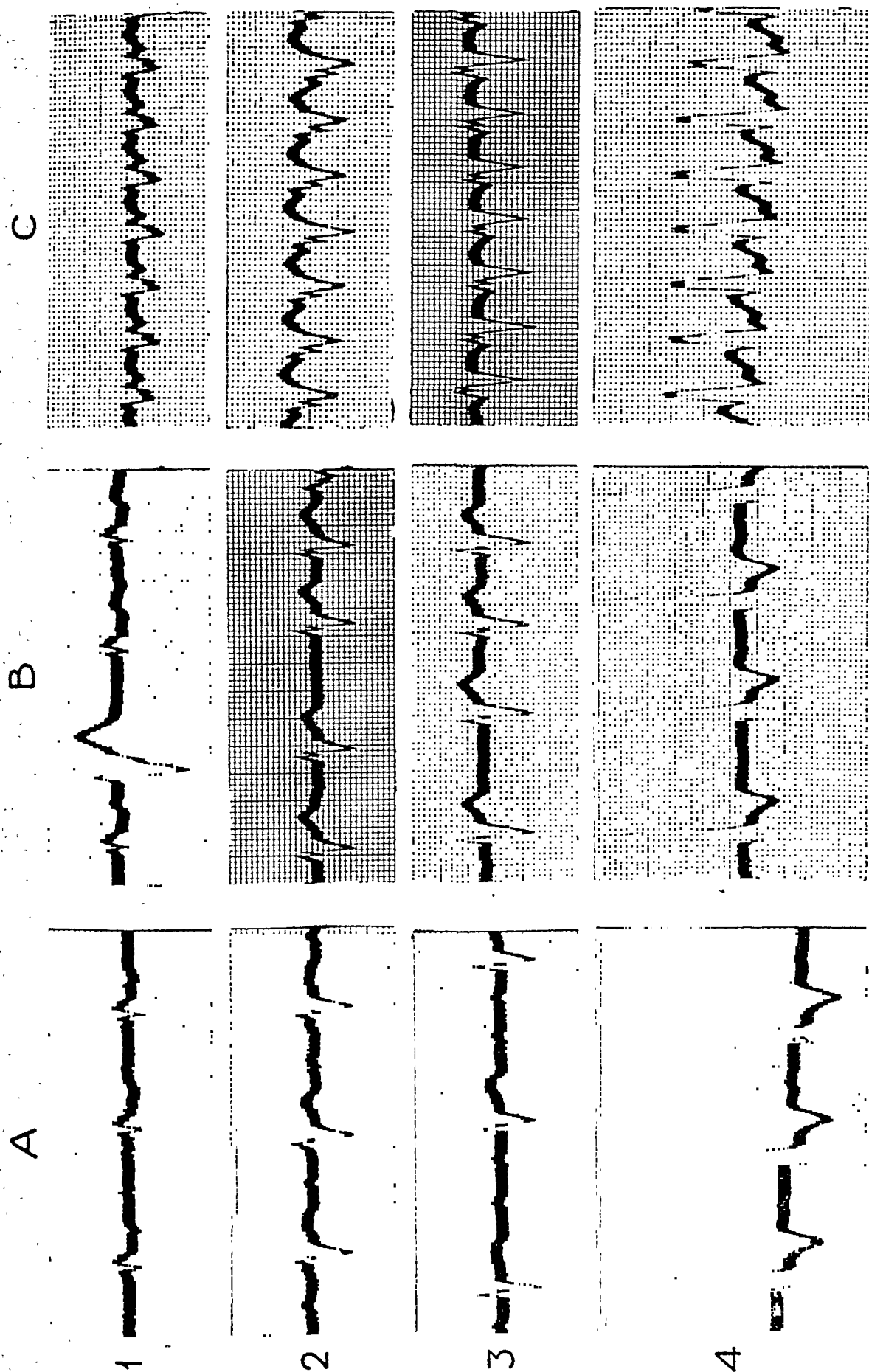
Fig. 4.—Electrocardiograms in Case 8. *A*, Aug. 15, 1936: complete A-V block and left bundle branch block in the three standard leads; auricular rate 130; ventricular rate 58. In Lead IV,* auricular fibrillation is present, with more rapid ventricular rate. The record indicates advanced myocardial damage. No digitalis or quinidine had been given. *B*, Oct. 16, 1936: auricular fibrillation, ventricular premature beats and left bundle branch block; ventricular rate 75. The general form of the ventricular complexes shows no marked change. *C*, Nov. 10, 1936: ventricular tachycardia; rate 160. Patient died twenty-two hours later.

*The precordial electrode was at the apex, the indifferent electrode on the left leg. T, according to the technique used, was normally inverted.

playing games. At 52 years of age, she was told that her heart was large, but she was not incapacitated. The blood pressure had been taken repeatedly and was always said to be normal. Seven years before, an electrocardiogram showed no abnormal changes. For the preceding six years she had been under the observation of Dr. H. E. B. Pardee, who found cardiac enlargement, intraventricular block in the electrocardiogram, and, under the fluoroscope, saw a knoblike shadow projecting from the right side of the heart. There were no evidences of congestive failure.

Six months before admission she suddenly developed an attack of precordial oppression and dyspnea. The heart rate was over 200. At the end of an hour, and after a hypodermic injection, it fell to 90. After that attack she was a cardiac invalid, and had dyspnea, edema, and three attacks of pulmonary congestion with fever up to 103° F. She had taken digitalis, scillaren, and ammonium chloride.

Examination showed dyspnea, but no cyanosis. There was slight edema of the ankles and sacral region. There were crackles at the bases of both lungs. The heart was enlarged, extending to the left anterior axillary line. The rhythm was regular, the rate, 42. The sounds were of fair quality; a soft systolic blow was heard at the apex. The liver was markedly enlarged. The radial arteries were thickened. The blood pressure on admission was 140/105. Subsequent readings ranged from 135 to 116, systolic, and 90 to 66, diastolic.

The blood cell count was normal. The Wassermann reaction of the blood was negative. The blood urea was 35 mg. per 100 cubic centimeters. A roentgenogram of the heart showed the transverse diameter to measure 17.2 cm.; the internal diameter of the chest was 22.3 centimeters. There was slight calcification of the aortic knob. Fluoroscopic examination showed a hump in the contour of the right border anterolaterally, suggesting to the roentgenologist an aneurysm of the right ventricle or an intrapericardial aneurysm low in the aorta. The electrocardiogram, on admission, showed sinus rhythm with prolonged A-V conduction and left bundle branch block. The P-R interval was 0.33 second, QRS, 0.15 second. The T wave was inverted in Leads I and II, upright in Lead III, and inverted in Lead IV. During the period of observation, complete A-V heart block developed, with, at times, auricular fibrillation and flutter. There were also paroxysms of ventricular tachycardia, which responded to quinidine therapy (Fig. 4).

For a time, myocardial function improved. A skin rash appeared, and was regarded as a toxic dermatitis of unknown cause. The temperature for several weeks ranged from normal to 100.2° F., rising shortly before death to 104.4°. The cause of the fever was unexplained. A blood culture was negative. Two days before death, there were signs of right hemiplegia with left facial palsy. Two months after entering the hospital she died during a paroxysm of ventricular tachycardia.

Clinical Diagnosis.—Arteriosclerotic heart disease; cardiac hypertrophy; cardiac insufficiency: bundle branch block; auricular fibrillation; auricular flutter; ventricular tachycardia; embolus to right lenticulostriate artery by infected thrombus: undiagnosed condition of skin; fever of unknown origin.

Autopsy No. 12274.—Heart: Weight, 440 grams. It was uniformly enlarged; the apex was formed by both ventricles, but principally by the left. Many subepicardial petechiae were seen along the distribution of the coronary arteries over the ventricles. All of the chambers

of the heart were enlarged. The walls of the auricles did not appear to be hypertrophied; those of the ventricles were somewhat thickened, that of the right ventricle measuring 5 mm., the left, 15 millimeters.
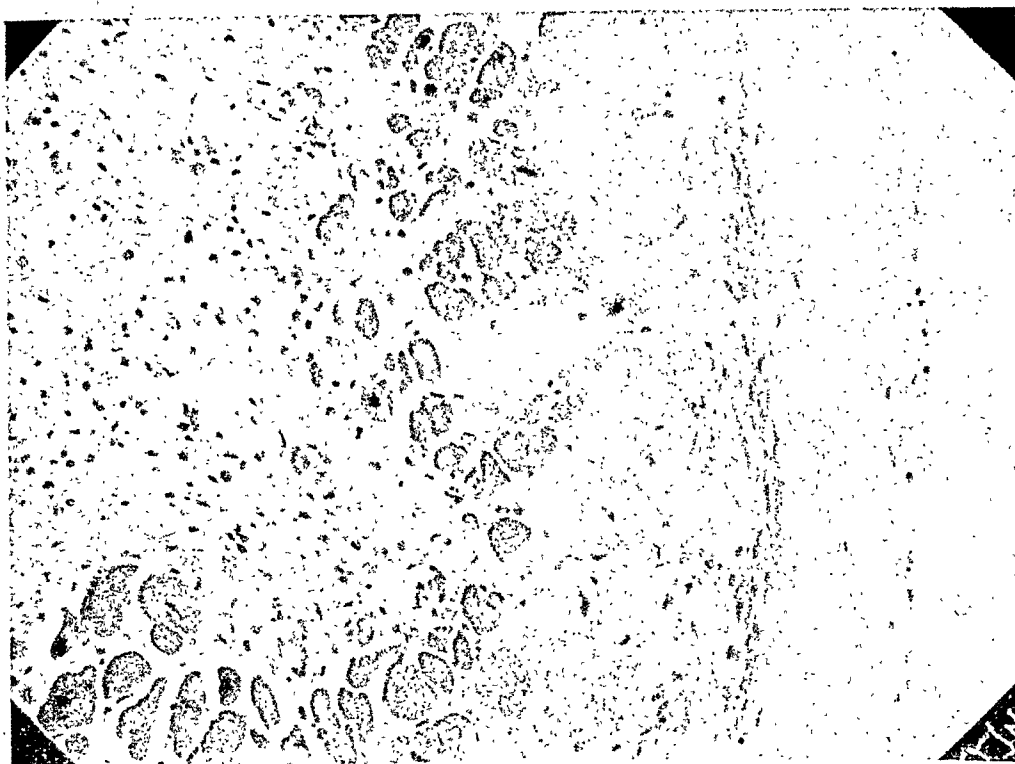
Fig. 5.—Case 8. Hypertrophy and necrosis of myocardium. Necrosis extends into conduction bundle (section from interventricular septum).
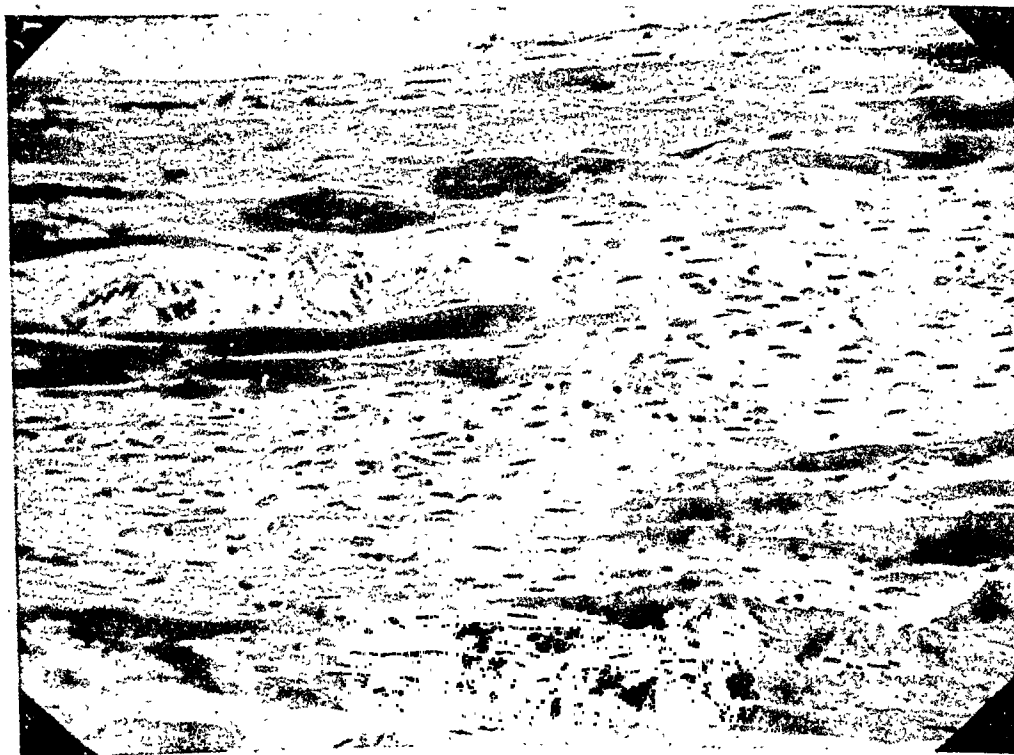
Fig. 6.—Case 8. Hypertrophy of myocardium and scar of an area of previous necrosis.

All of the papillary muscles were moderately enlarged. The tricuspid, pulmonic, and mitral valves were normal; the chordae tendineae were delicate. There was some thickening of the base of each aortic cusp;

the remaining portion of the leaflets was normal. The myocardium o both ventricles was firm and reddish-brown. Fine, greyish streaks were present in the myocardium of the left ventricle, and the septal muscle was mottled with yellowish-grey areas. The endocardium over the septum was thickened below the aortic valve; elsewhere it was normal. Only a few, very small, yellowish areas were found in the intima of the coronary arteries.

Aorta: Small, slightly raised, yellowish-grey plaques were present in the intima of the ascending portion. Similar areas were more numerous in the abdominal segment of the aorta, where a few of them were ulcerated.

Histologic Examination.—Heart: The myocardium of both auricles was hypertrophied and diffusely scarred. In the right ventricle there were areas of recent necrosis where the muscle was homogeneous, stained deeply with eosin, and did not show any nuclei. These necroses frequently involved the branches of the conduction system.

Numerous areas of necrosis were seen in the interventricular septum. These areas were of variable size, and often extended into the conduction bundle (Fig. 5). In addition, there were scars composed of loose connective tissue (Fig. 6). Phagocytes filled with pale-yellow, granular pigment were present in the scars. Changes similar to those in the septum occurred in the left ventricle and papillary muscle, and the necroses and scars frequently extended into the conduction fibers.
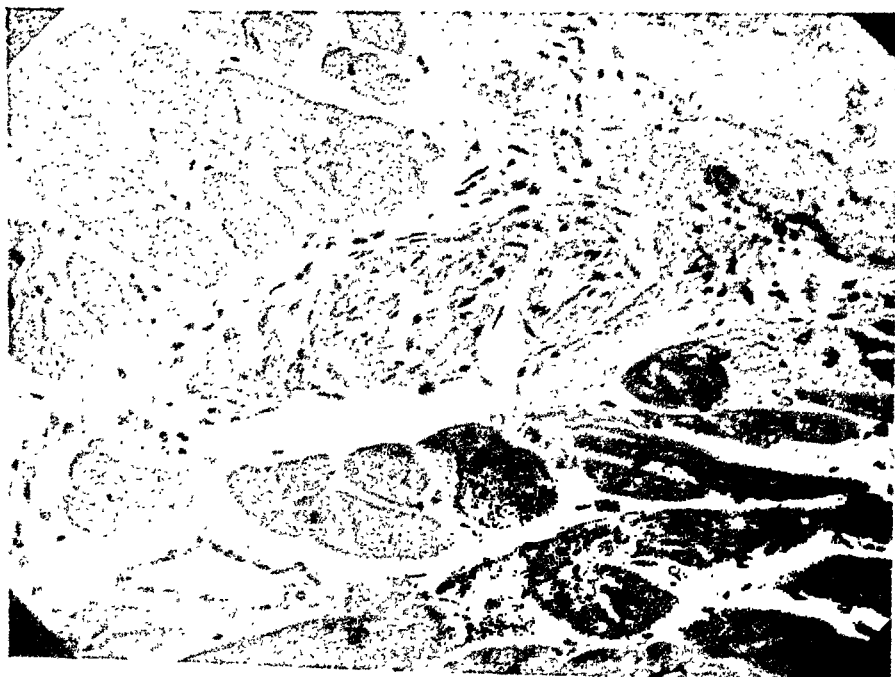
Fig. 7.—Case 5. Slight sclerosis of arteriole in myocardium.

In all of the sections, aggregates of small mononuclear cells were clustered about or near some of the arterioles. Only rarely was there an arteriole with a thickened intima. and in such arterioles this alteration was slight; it did not affect the entire intima, and the lumen was not appreciably narrowed (Fig. 7).

Aorta: The only lesion was that of moderately advanced atherosclerosis.

Final Note.—This was an interesting and rather obscure case of an elderly woman who for a number of months had had attacks of parox-

ysmal tachycardia and, toward the end of her life, electrocardiographic changes showing, at times, complete, and at other times, partial, heart block. The case was looked upon as one of coronary sclerosis and myocardial damage, but this was not confirmed by the autopsy. In both ventricles there were numerous patches of recent necrosis with little or no cellular reaction, together with older and more recent scars. There was a history of diphtheria followed by edema and temporary cardiac embarrassment. This occurred when the patient was 7 years old, and there was a long interval during which she was free from cardiac symptoms. It seemed farfetched to refer the myocardial scars to a past diphtheritic myocarditis, and certainly one must seek another explanation for the recent necroses.

Anatomic Diagnosis.—Necroses of myocardium, healed and recent; cardiac hypertrophy and dilatation; chronic passive congestion of lungs; lobular pneumonia, confluent; focal necroses of liver; acute splenic tumor; encephalomalacia, internal capsule, left; toxic erythema; infarcts of kidneys, healed; cholelithiasis.

CASE 9.—Unit No. 392348. T. I., a Negro man, aged 38, married, an unemployed longshoreman, was first admitted to the hospital on Sept. 25, 1933, complaining of shortness of breath, cough, and attacks of nocturnal dyspnea. His general health was good. At the age of 18 years he had a chancre, and also gonorrhea with inguinal abscesses. Specific intravenous therapy was given for a short time. He was refused for Army service in 1918 (aged 23 years) because of "heart trouble." He was in the habit of drinking plenty of whiskey, but the amount was not stated.
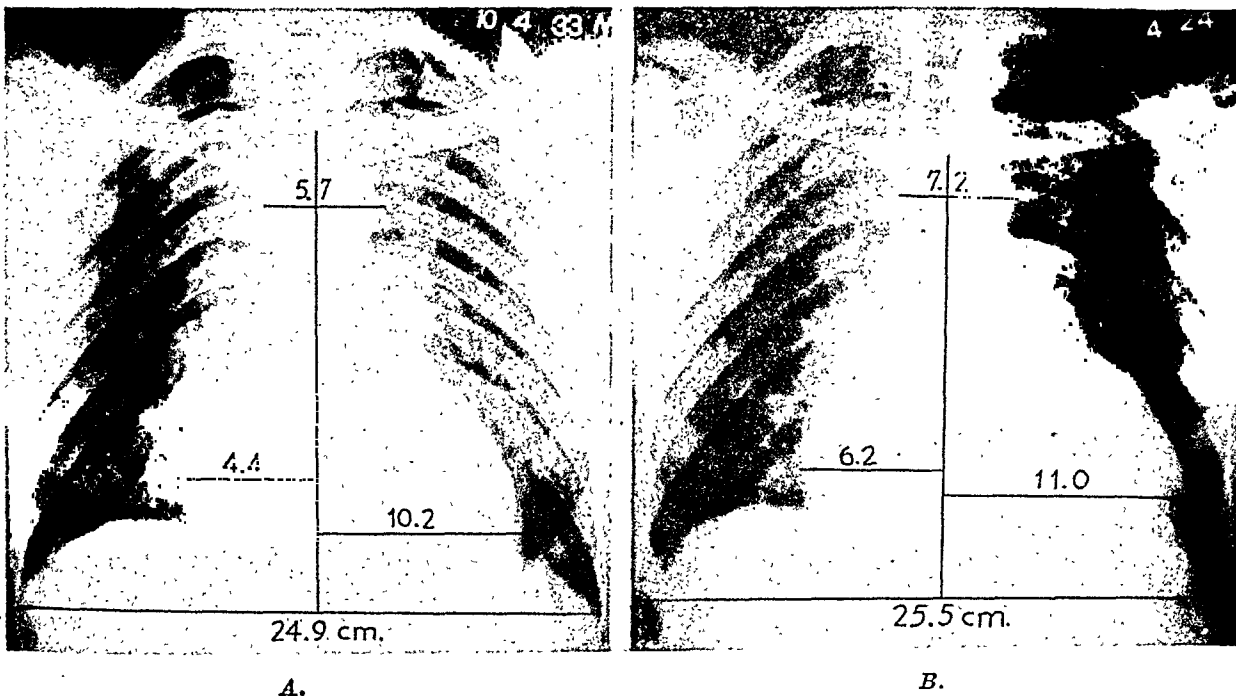
Fig. 8.—Case 9. Teleroentgenograms showing increase in size of heart in course of two and one-half years. *A*, Oct. 4, 1933: two months after onset of symptoms. *B*, April 24, 1936: six months before death.

Six weeks before admission, dyspnea, cough, and nocturnal attacks of asthma began and increased rapidly in severity. For three weeks the ankles and legs had been swollen.

Examination showed moderate dyspnea on effort. There were râles at the bases of both lungs. The heart was enlarged. The rhythm was

regular save for a few premature beats. A gallop was heard. The liver was enlarged. There was brawny edema of the legs up to the mid-thighs; the scrotum was swollen. The blood pressure was 120/85. The retinal vessels were not sclerotic.

The Wassermann and Kahn reactions of the blood were strongly positive. The spinal fluid Wassermann was negative. An electrocardiogram showed sinus rhythm with low voltage. The P-R interval measured 0.17 second. The T wave was inverted in the three standard leads. The blood cell count was normal. A roentgenogram of the heart showed the transverse diameter to measure 14.6 cm.; the internal diameter of the chest was 24.9 cm. (Fig. 8). The sedimentation rate of the erythrocytes was 19 mm. in one hour. There was no fever. The blood pressure fell to 90/70; on discharge it was 104/72.

The usual cardiac therapy was followed by improvement. Intramuscular injections of bismuth were begun, and iodide was given by mouth. He was sent home at the end of five weeks, with compensation recovered.

In the course of the next three years, the patient was admitted to the hospital five times at intervals of several months, on each occasion with myocardial insufficiency. Antisyphilitic treatment was continued in the out-patient department, in courses. In December, 1934, bundle branch block appeared for the first time in the electrocardiogram. Low voltage was no longer present. The QRS interval measured 0.12 second. The T wave was inverted in Lead I and upright in Leads II and III. Bundle branch block persisted from this time until death, with occasional premature beats interrupting the regular rhythm (Fig. 9). The gallop also continued to be heard. The blood pressure remained low. The Wassermann reaction was always strongly positive.

On April 10, 1936, one of us (R. L. L.) made the following note: "Symptoms began at the age of 38 years. There has been no consistent elevation of blood pressure. The evidence for the existence of a syphilitic myocarditis is slender; by most pathologists, this form of diffuse myocarditis is not recognized. Coronary sclerosis is a possibility, although because of the course, is unlikely to be present. Cardiac enlargement has always been conspicuous. The electrocardiographic changes and repeated attacks of congestive failure indicate a seriously damaged myocardium. The blood pressure today is 114/90. There is a marked protodiastolic gallop.

"This case, it seems to me, must be classed in the group described as 'hypertrophy of unknown etiology,' in which the lesions in the heart muscle vary in character and degree. The immediate prognosis for this bout is good. Within two years, I believe the course will be run."

The final admission was on Oct. 20, 1936. Congestive failure was marked. The temperature rose to 102.8° F. There were signs of diffuse, bilateral bronchopneumonia. The leucocytes numbered 14,500, with 84 per cent polymorphonuclears. He was irrational and failed steadily. He died thirty hours after entering the hospital, at the age of 42, having had symptoms for a little over three years.

Clinical Diagnosis.—This varied on different admissions to the hospital. The following were included: Syphilis; syphilitic aortitis; narrowing of coronary artery due to syphilis; generalized arteriosclerosis; arteriosclerotic heart disease; sclerosis of coronary arteries; fibrosis of myocardium; cardiac enlargement; cardiac insufficiency; syphilitic myocarditis; bronchopneumonia, organism unknown.

Autopsy No. 12256.—Heart: Weight, 570 grams. The epicardium was thickened over the coronary arteries. The cavities of the right
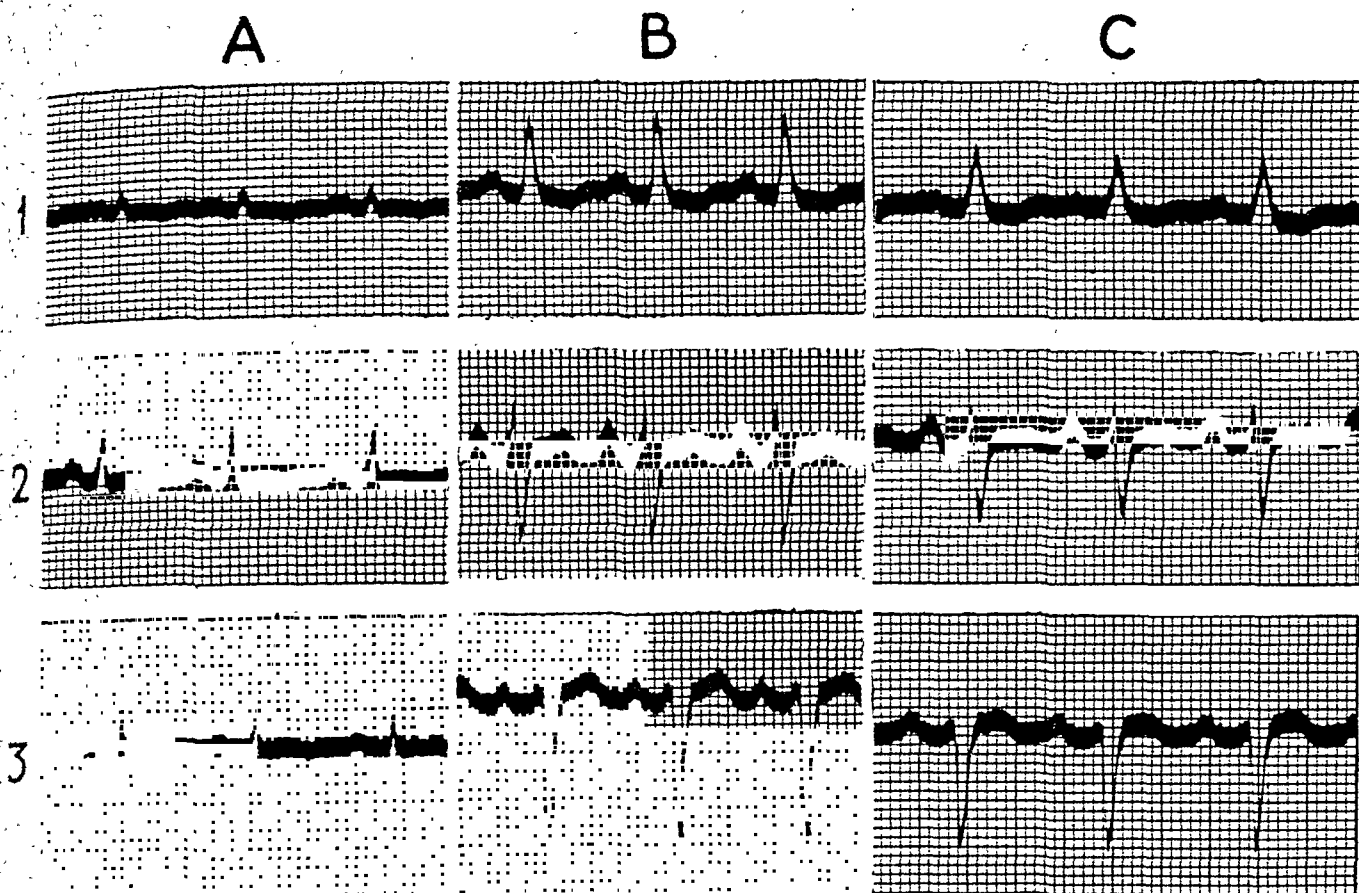
Fig. 9.—Electrocardiograms in Case 9. *A*, Sept. 26, 1933: sinus tachycardia; rate 108. P-R = 0.16 second. Low voltage, with inversion of T waves in all leads. No digitalis taken. *B*, Dec. 29, 1934: left bundle branch block; rate 100. P-R = 0.16 second; QRS = 0.12 second. Conspicuous changes have occurred since record made three months earlier. *C*, Aug. 11, 1936: left bundle branch block; rate 90. P-R = 0.20 second; QRS = 0.12 second. Only slight changes have taken place since record made nineteen months before. Patient died three weeks later.
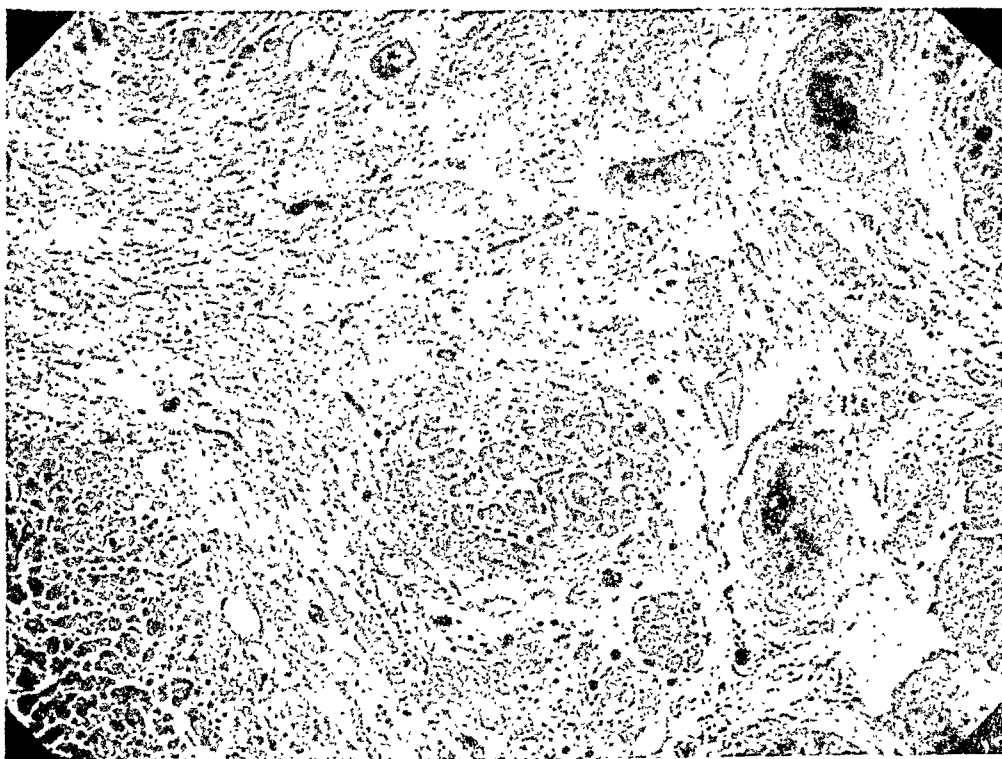
Fig. 10.—Case 9. Hypertrophy of myocardium with fibrosis.

auricle and ventricle were greatly dilated. In the auricular appendage there was a small thrombus. The tricuspid and pulmonic valves were normal. The left auricle was markedly dilated. The edges of the mitral leaflets, at the right juncture of the cusps, were moderately thickened. A few of the chordae tendineae inserting into these parts of the leaflets were thickened; the other chordae were normal. The papillary muscles were moderately hypertrophied. The aortic valve was normal. The myocardium was a pale, greyish red, with many pinkish-grey scars in the left ventricle. Below the aortic ring there was a greyish-white scar, 2 cm. in diameter. The wall of the right ventricle was 6 mm. thick, and that of the left, 14 to 20 millimeters. The coronary arteries were strikingly free of atheroma and were entirely normal.

Aorta: There was surprisingly little atheroma; only a few fatty plaques were found in the abdominal portion of the vessel.

Histologic Examination.—Heart: The myocardium was hypertrophied. Scars of varying sizes were found in the walls of both ventricles and the interventricular septum. The scars were compact, and but slightly vascularized (Fig. 10). Near the vessels at the margins of the scars there were sparse collections of lymphocytes. The arteries and arterioles were normal. The thrombus in the right auricular appendage was in process of being organized. The myocardium beneath the thrombus was hypertrophied but not scarred.

Aorta: The intima was slightly thickened by fibrillar material. The media and adventitia were normal.

Final Note.—There were none of the obvious causes of myocardial fibrosis, neither syphilis, coronary sclerosis, nor clear evidence of old rheumatic disease. There was no syphilitic aortitis. One is driven to assume that the lesions represented healed myocarditis of unknown cause.

Anatomic Diagnosis.—Myocarditis, obsolete (?); fibrosis of myocardium; cardiac hypertrophy and dilatation; thrombus in auricle, right; infarct of lung and spleen; chronic passive congestion of viscera; encephalomalacia, cerebellum, right; ascites; hydrothorax, bilateral; edema of ankles; cholelithiasis.

CASE 10.—Unit No. 259359. E. S., a Negro man, aged 43 years, married, a porter, was first seen in the Vanderbilt Clinic on June 12, 1930, complaining of epigastric pain. He had pneumonia at 41, and a chancre at 42 years of age, for which five or six treatments were given. He took a pint of whiskey daily from 1900 to 1929; for the preceding six months he had taken three drinks a day and had gone on a drunken spree every two weeks. He smoked thirty cigarettes and chewed a plug of tobacco daily. Three months previously he noted dyspnea on effort and abdominal pain. He had lost 20 pounds in four years.

Examination showed an enlarged heart, with gallop rhythm at the apex. There were moist râles at the bases of both lungs. The liver was large and tender. The blood pressure was 96/80.

The Wassermann reaction of the blood was positive (2 plus with the alcoholic antigen and 4 plus with the cholesterin antigen). A roentgenogram of the heart showed the transverse diameter to measure 16.3 cm.; the internal diameter of the chest was 24 centimeters. The electrocardiogram showed sinus rhythm with left bundle branch block.

He received five courses of bismuth by intramuscular injection between July, 1930, and July, 1933. He was also given digitalis and

potassium iodide. During these three years he got along fairly well, although he was unable to work because of exacerbations of dyspnea and precordial pain. Frequent, severe, sore throats and cough aggravated the symptoms. For this reason, in December, 1932, tonsillectomy was performed. At that time, the electrocardiogram resembled the one made eighteen months previously. The heart was larger. The blood pressure ranged from 130 to 90, systolic, and 80 to 60, diastolic. The basal metabolic rate was –5 per cent.

There were three subsequent admissions to the hospital on account of recurring and progressively severe myocardial insufficiency. The blood urea was slightly elevated during decompensation, but returned to normal after improvement. The form of the electrocardiogram did not change. The Wassermann reaction was now negative; the Kahn reaction was faintly positive. The levels of the blood pressure were as described. On one occasion he coughed up bloody sputum and there was elevation of temperature, presumably because of pulmonary infarction.
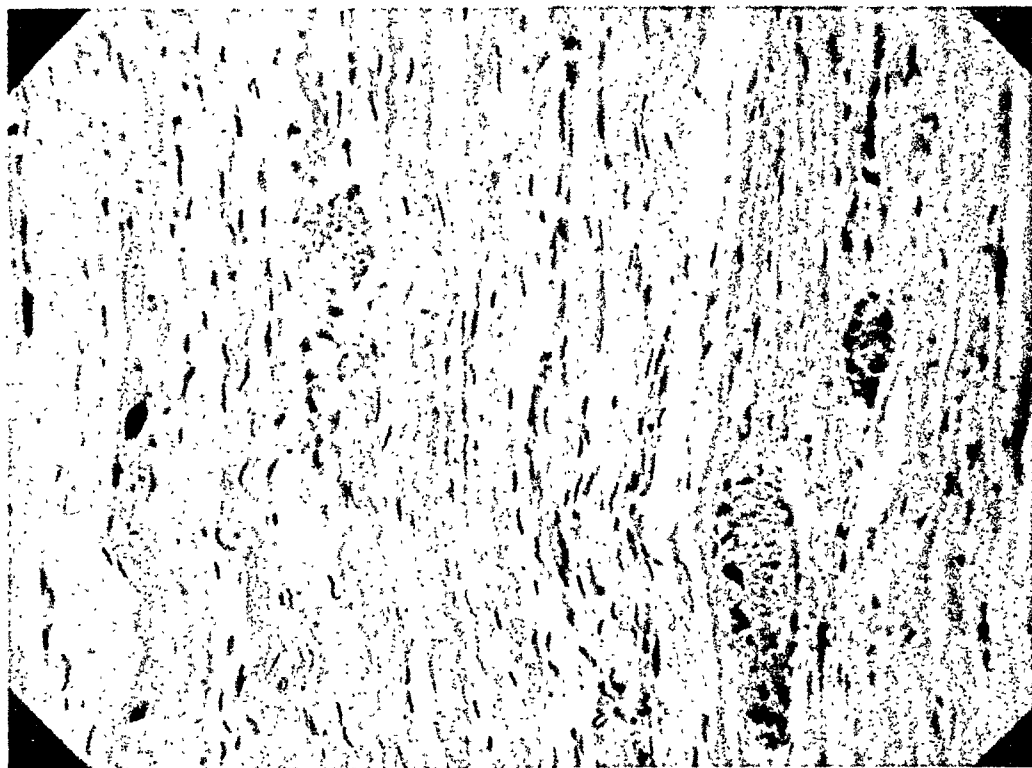
Fig. 11.—Case 10. Hypertrophy of myocardium with fibrosis.

He was brought to the hospital on Nov. 12, 1934, in a semicomatose condition. Hyperpnea was marked. The venous pressure was 16 cm. of water. The leucocyte count was 19,500. He presented the picture of shock. The temperature rose steadily to 105° F., and he died in coma five days after entering the ward and four and one-half years after the onset of symptoms.

Clinical Diagnosis.—Enlarged heart, cause unknown; infarction of myocardium due to arteriosclerotic coronary thrombosis; infarction of lungs, embolic; bronchopneumonia; Wassermann reaction, positive.

Autopsy No. 11665.—Heart: Weight, 490 grams. It was very large as compared with the size of the body. The apex was formed by the left ventricle. Many small recent hemorrhages were seen beneath the epicardium of the auricles and their appendages. The right auricle

and ventricle were dilated. At the apex, the wall of the right ventricle measured only 1 mm. in thickness, although in other parts the ventricular wall was as much as 8 mm. thick. A thrombus was found at the apex between the columnae carneae. The tricuspid and pulmonic valves were normal. The left auricle was moderately dilated. The left margin of the anterior leaflet and the adjacent portion of the posterior cusp of the mitral valve were thickened, and the chordae tendineae inserting into these parts of the leaflets were thicker than normal. The papillary muscles were hypertrophied. The left ventricle was enormously dilated; its wall measured from 12 to 20 mm. in thickness. At its apex the columnae carneae were thinner than normal. The aortic cusps were slightly thickened in their basal portions. The endocardium throughout the heart was normal except for some opaque streaks and yellowish areas over the septum of the left ventricle. The myocardium was brownish red and had a coarse texture. Except for some tortuosity, the coronary arteries were normal.

Aorta: A few yellowish, atheromatous plaques were present in the intima of the posterior wall.

Histologic Examination.—Heart: In all of the sections the myocardium showed the usual characteristics of hypertrophy. One section from the left ventricle passed through an area in which the muscle had been replaced by a broad, compact scar in which there were only a few capillaries (Fig. 11). Near the margin of the scar was a small vein with an accumulation of lymphocytes about it. In a second section collagen separated the myocardial fibers, but did not replace any of them. On the endocardial surface there was an organizing thrombus. The muscle beneath the thrombus was unaltered except for hypertrophy.

A section from the apex of the right ventricle disclosed diffuse scarring of the myocardium near the epicardial surface. The endocardial thrombus was in process of being organized. The myocardium immediately beneath the thrombus was diffusely infiltrated with small mononuclear cells, but was not scarred. In all of the sections the coronary arterioles were normal.

Aorta: The media and adventitia were normal. The intima was moderately thickened by fibrillar tissue.

Final Note.—This case seems to fall into the category of unexplained cardiac fibrosis, with hypertrophy and dilatation. All of the usual causes of cardiac hypertrophy could be excluded, namely, hypertension, renal disease, thyroid disease, and syphilis. The coronary arteries and arterioles were normal. There were slight valvular lesions suggesting rheumatic disease, but the distribution and extent of the scarring were not suggestive of old rheumatic myocarditis. The most plausible view would be that the scarring was the result of an old, acute myocarditis. The other lesions in the case were of subordinate interest.

Anatomic Diagnosis.—Cardiac hypertrophy and dilatation; fibrosis of myocardium; thrombus in ventricle, right; infarcts of lungs; chronic passive congestion of viscera; lobular pneumonia.

CLINICAL FEATURES

There were eight males and two females, ranging in age, at death, from 29 to 66 years. Six were white and four were Negroes. The duration of symptoms from onset to death ranged from ten days to

five years, but eight of the patients lived only eight months after the onset of discomfort. There were no specific antecedent infections common to the group. Two patients were markedly alcoholic; these were male Negroes with positive Wassermann reactions. There were no apparent dietary deficiencies and signs of avitaminosis were not noted.

In each case the symptoms were those of myocardial insufficiency. Various types of arrhythmia were commonly observed; paroxysms of tachycardia occurred in two cases. Abdominal pain was a complaint in three. Cardiac pain of the anginal type was conspicuous by its absence; mild substernal discomfort was mentioned by two patients.

The heart sounds were weak, and gallop rhythm was frequently present. There were no murmurs of valvular disease. The blood pressure was normal or low, save for occasional slight transient elevations during the acute phases of cardiac failure. The Wassermann reaction of the blood was negative in seven, positive in two, and not known in one.

Electrocardiograms were taken in seven cases; three patients died in the first twenty-four hours after admission to the hospital, and a tracing was not made. All of the records showed deviations from the normal; the changes varied according to the extent of the lesions in the heart. In the cases in which there was no fibrosis the changes were slight; in the presence of advanced fibrosis they were extreme. Actively progressive myocardial damage was reflected in the altering form of the complexes and in many types of irregularity. These included inversion of T in Lead I, or in Leads I and II; low voltage; premature beats; auricular fibrillation, both paroxysmal and permanent; paroxysmal auricular flutter; paroxysms of tachycardia originating in the auricles, junctional tissues, or ventricles; and partial and complete A-V block. In three cases bundle branch block developed in the course of the illness and persisted until death.

A noteworthy feature was the occurrence of embolism, arising apparently from mural thrombi in the heart. Infarction of the lungs occurred six times, of the kidneys, four times, and of the spleen, once. In one case there was embolic occlusion of the central artery of the retina.

Death took place as the result of gradually progressive, often recurring, cardiac insufficiency in seven patients; three died suddenly.

In only three of our cases was the correct diagnosis made prior to the autopsy, and this was done by a process of exclusion. The condition which most frequently gave rise to confusion was arteriosclerotic heart disease, in which the signs of coronary insufficiency were not manifest and the true nature of the basic disturbance was apparent only at the post-mortem table. On occasion, instances of coronary thrombosis and atypical rheumatic carditis were regarded as examples of this syndrome until direct examination of the heart was made.

A consideration of etiology is unprofitable because facts are lacking, but a brief reference to the possible role of dietary deficiency is pertinent because of current interest in this field. No signs of a lack of vitamin B_1 were observed, and polyneuritis was notably absent. It is rare to see an advanced degree of beriberi heart disease without involvement of the peripheral nerves. Vitamin therapy was not tried in our patients, yet there were remissions, for which slight modifications in dietary habits could hardly be held accountable. One of von Bonstorff's patients failed to improve after receiving large doses of crystalline thiamine.

Myocardial lesions, consisting of necrosis of the muscle fibers, followed by scarring, have been produced in rats and hogs by a diet markedly deficient in potassium.[17, 18] A relationship between these experimentally induced lesions and similar changes in human hearts has not been demonstrated.

<div align="center">PATHOLOGY</div>

There are several features common to these ten cases. The first is the absence of advanced sclerosis of the coronary arteries. In some of the cases these arteries were normal, whereas, in the remainder, only sclerosis of mild degree was present. In none were the lumina of the arteries compromised, nor was there any calcification or thrombus formation. The orifices of the arteries were not narrowed. Rarely was there any thickening of the intima of the coronary arterioles, and, when this was present, it did not involve the intima of the entire circumference at any one level, but was localized to a small segment, and only slightly reduced the lumen of the arteriole. These mild changes in the arteries and arterioles were too insignificant to be held responsible for any lesions found in the myocardium.

It may be added that in no single case was there generalized arteriolar sclerosis. Such atherosclerosis of the aorta as was present was not of marked degree and, indeed, in many of the cases, it was less than might reasonably have been anticipated from the ages of the patients. Furthermore, in those cases in which the blood showed a positive Wassermann reaction, anatomic evidence of syphilis was entirely lacking.

Another feature was the hypertrophy of the myocardium that, although variable in degree, existed in each case. The myocardial fibers showed the usual evidences of hypertrophy, namely, increased size, with enlargement, hyperchromatism, and altered shape of the nuclei.

In Cases 1, 2, 3, and 4, examination revealed only hypertrophy of the myocardium without any scarring, either gross or histologic. A careful review of all of the lesions found in these cases at autopsy does not disclose any that could be held accountable for the cardiac hypertrophy.

An insignificant increase of stroma in the myocardium was found in two cases (5 and 6). This was laid down between the myocardial fibers and did not replace any of them. It would seem most unlikely that this could in any way have been responsible for the hypertrophy; indeed, it is more probable that this increased supporting tissue between the myocardial fibers was secondary to the hypertrophy, as is so often the case.

More extensive lesions were present in the hearts from Cases 7, 8, 9, and 10. In the first two cases of this group (7 and 8) the myocardium had undergone recent necrosis. The appearance and distribution of the necrotic areas in the first of these two (7) suggested infarction, although no cause for this was found. The necrotic muscle impinged on the conduction bundle branches.

In the second of these two cases (8) the necrosis was very widespread; it was found in the walls of both ventricles and in the interventricular septum. It was very evident that in all of these situations the conduction fibers were frequently involved. Areas of scarring indicated the sites of previous necroses, and these resulting scars appeared to be of different ages, for some were compact and others looser in texture. Near the arterioles, in the neighborhood of the necrosis and scars, small aggregates of lymphocytes were gathered. These cell accumulations were not regarded as evidence of syphilis, but as part of the reaction to the necrosis. The history, the negative Wassermann reaction, and the absence of any anatomic evidence of syphilis oppose the possibility that the cardiac lesions could have been of syphilitic origin.

The two remaining cases (9 and 10) are examples of extensive scarring without any demonstrable cause, both occurring in patients with positive Wassermann reactions. Over quite large areas the cardiac muscle had been replaced by compact scars. In one of these cases (9), sparse perivascular accumulations of lymphocytes were found near the scars; these were interpreted as secondary to the myocardial damage and not as indicative of the etiology of the lesion. Careful study of the various viscera did not reveal any evidence of syphilis, and the myocardial changes were not believed to be syphilitic.

In the other of these two cases (10) there were large myocardial scars without any perivascular lymphocyte collections. Here also, although the Wassermann reaction was positive, there was complete absence of any lesions in other organs that could be interpreted as syphilitic, and it does not seem plausible that the myocardial scars were due to a previous syphilitic myocarditis.

The scarring in Cases 9 and 10 might conceivably have resulted from necroses similar to those described in Case 8, although no suggestion can be made as to what produced the lesions in these three hearts, for the common causes would seem to have been completely eliminated.

The lesions were not the same as those that have been described in syphilitic myocarditis.

Thrombi were found in six of the ten hearts, twice in the right auricle, twice in the right ventricle, and four times in the left ventricle. Histologic studies of the myocardium and endocardium beneath the thrombi gave no clue as to what initiated the formation of the thrombi. The endocardium beneath the thrombi was either normal or, when abnormal, the changes were clearly related to the process of organization of the thrombi. The myocardium was hypertrophied but not scarred or necrotic immediately beneath the thrombi. As might have been expected, these thrombi were the sources of emboli, and infarcts were discovered in the lungs in each case, in the kidneys in four, and in the spleen in one.

Finally, it may be noted that there were no valvular lesions that could have played a role in the production of the hypertrophy. There were five instances in which the mitral leaflets were altered, and in these the lesion was not sufficient to have disturbed the competent closure of the valve cusps. The same was true in those cases in which the aortic cusps were thickened at their bases.

There was only one instance of pericardial adhesion (Case 2). The adhesion covered only a small area of the posterior surface of the heart, and it is most unlikely that it could have exerted any effect that would have resulted in the hypertrophy.

SUMMARY

These cases appear to form a clinical group of which the chief features are: marked cardiac hypertrophy; symptoms of cardiac insufficiency; occurrence of various types of arrhythmia; frequent emboli to the pulmonary and systemic circulations; rapidly progressive course after the onset of symptoms; and death from gradual cardiac failure or in sudden fashion. The cause of the syndrome is unknown.

The hearts, at autopsy, all show hypertrophy of the muscle fibers. In some cases, this is the only lesion. In others there is also fibrosis, which, in different instances, may be slight or extensive. There may be areas of necrosis, both old and recent. Intracardiac thrombi are often present.

Whether these cases represent a single disease picture, observed at different stages of its development, or are to be regarded as of heterogeneous origin, cannot now be stated. Only a knowledge of the etiology can furnish an answer to this question.

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UNUSUAL CONDITIONS INVOLVING THE ABDOMINAL AORTA

Seven Cases With Autopsy Observations

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VARIOUS diseases of the abdominal aorta are associated during their course with dramatic symptoms. They are also of unusual interest because of their rarity and difficulty of diagnosis. We have been fortunate in accumulating seven cases of unusual conditions involving the abdominal aorta, with autopsy observations. These include mycotic aneurysm and involvement by tuberculosis and malignant tumors.

I. MYCOTIC ANEURYSM

The following are two very similar cases of rupture of the abdominal aorta due to a rare and unusual etiological factor. An ante-mortem diagnosis was made in one of the cases.

CASE 1.—J. C., a 30-year-old Italian printer, was admitted with a chief complaint of swelling of his joints for three weeks. One month previously, he had a streptococcus sore throat. The next day his left knee became swollen, and this was followed by right ankle and knee involvement in a few days. He was given three different sulfonamide derivatives with some remission. During the last few days before admission the symptoms recurred and he was hospitalized. He had had pneumonia complicated by rheumatic fever six years before.

Examination.—Examination revealed a well-developed man who did not appear acutely ill. The fundi were negative. The pharynx was slightly reddened, but there was no cervical lymphadenopathy. The heart was of normal size and regular. The blood pressure was 120/80. There were soft systolic apical and basal murmurs. There was fluid in both knee joints, with a floating patella on the left. The left ankle was reddened, hot, and swollen. The clinical impression was acute rheumatic fever.

Course.—On salicylates, the temperature fell in two days from 101° to 99° F., but rose two days later to 104° F., where it remained until the end. Although the pulse rate and sedimentation rate were still rapid, the joint swelling and heart murmurs improved. On the third day, severe pain appeared over the left sacroiliac joint, with tenderness but no swelling. On the seventh day he developed numbness down the left thigh and leg, with absent knee jerk and definite muscle weakness. All other sensations and reflexes were unimpaired except for hyperesthesia from the second lumbar spine downward. The clinical impression was psoas abscess. Blood cell counts at this time revealed a moderate secondary anemia and 28,350 leucocytes, with 95

per cent polymorphonuclear neutrophiles. On the ninth day he developed a friction rub over the left anterior axillary line, with occasional crackling râles. Fullness appeared in the left flank which was described on the tenth day as a small, tender, hard mass in the left lumbar region. On the twelfth hospital day a nonfading, petechial macular eruption appeared over the lower abdomen and extremities. They measured 1 to 5 mm. in diameter. Paralysis of the left lower extremity became complete. He developed an unrelieved hiccup. On the seventeenth hospital day, marked scleral jaundice appeared, but the liver and spleen were not palpated. The van den Bergh reaction was direct, the icteric index, 42, and the serum bilirubin, 4.5 mg. per 100 c.c. of blood. A blood culture at this time revealed *Streptococcus hemolyticus*. Two subsequent cultures corroborated this finding. The heart became enlarged to the anterior axillary line, and there were a double murmur at the apex and a soft systolic murmur at the pulmonic area. On the eighteenth hospital day, bilateral basal râles appeared, with fluid at the left base. A pericardial friction rub was heard to the left of the sternum. The firm tender mass in the left flank became very pronounced, and transmitted an impulse. On the twentieth day all joints became painful, especially the left wrist and elbow. Purulent material from the elbow yielded a culture of *Str. hemolyticus*. Diarrhea became pronounced, but stool culture was negative for the typhoid-dysentery groups. Thoracentesis on the twenty-fourth day revealed a hemorrhagic fluid, and Type VI pneumococcus was identified. The mass in the flank became markedly pulsating, transmitting a harsh systolic sound which radiated to the left. The patient became stuporous and died on the twenty-ninth day. The final diagnosis was mycotic aneurysm of the aorta, with possible dissection along its major branches and into the left subphrenic area retroperitoneally, with formation of a hematoma or abscess anterior to the left psoas muscle.

Further Studies.—The electrocardiogram showed left axis deviation. The transverse diameter of the heart was enlarged as would be expected with rheumatic mitral valvular disease. No osseous changes were noted in the left knee, ankle, or pelvis. The psoas muscle on the left was obscured by a shadow, with evidence of a soft tissue density at the lower portion of the left kidney suggestive of a mass or collection in the left retroperitoneal space. In the pyelograms, the medial outline of the left kidney appeared indistinct, and no dye excretion was visualized on this side. The blood and spinal fluid Wassermann reactions were negative. The blood uric acid, urea, sugar, and creatinine were 2.7, 29, 84, and 1.2 mg., respectively, per 100 cubic centimeters. Terminally, the urea and creatinine rose to 105 and 2.14 mg. respectively, per 100 c.c. of blood. The temperature ranged between 101° and 104° F.

Autopsy.—Autopsy revealed 250 c.c. of clear yellow fluid in the peritoneal cavity. The sternoclavicular joints and left knee contained pink, purulent fluid. Behind the manubrium was an abscess cavity, 3 cm. in diameter. There were seven small abscesses under the epicardium, but the heart itself was entirely negative. A large, firm, retroperitoneal mass protruded into the peritoneal cavity from the second to the fifth lumbar vertebrae, extending from the left flank to just beyond the right vertebral borders. About 5 cm. above the aortic bifurcation, the wall was necrotic and ruptured. It connected with the large sac containing friable tissue mixed with blood clots. Microscopically, the blood clots were degenerated without attempt at or-

ganization, and incorporated an occasional colony of hemolytic streptococci. There was slight atherosclerosis of the abdominal aorta, with extensive suppurative necrosis and an abscess in the adjacent tissue. In addition, there were hemorrhagic infarcts of the lung, kidneys, and spleen.

Final Diagnosis.—The final diagnosis was septicemia (blood cultures positive for *Str. hemolyticus*), with suppurative arthritis as the primary focus. This resulted in mycotic aneurysm of the abdominal aorta, with rupture; septic infarcts of the lungs, spleen, and kidneys; and suppurative myocarditis and abscess of the mediastinum.

CASE 2.—R. H. (case of Dr. H. Wolfer), a white man, aged 42 years, was admitted with pain in the hands of three weeks' duration. Three weeks previously he had developed pain and swelling in all the joints of the left arm. The right arm became similarly involved, and then the lower extremities, but these symptoms gradually disappeared except for a slight residuum in the right hand and knee and left shoulder. Twenty years before, he had had migrating joint pains which cleared up spontaneously.

Examination.—Examination revealed a well-developed man who appeared acutely ill. Except for a cataract on the left side, the head was negative. The neck, lungs, and heart were entirely negative. The blood pressure was 125/65. The right knee and hand and left shoulder and ankle were red, swollen, and tender. The temperature was 104° F. The diagnosis was acute infectious polyarthritis.

Laboratory Data.—These included a leucocyte count of 17,800, with 85 per cent polymorphonuclears; this rose to 22,700 four days later. Urinalysis, and the gonococcus fixation and Wassermann reaction were negative. The blood urea and uric acid were 40 and 3.6 mg. per 100 c.c. of blood, respectively. Roentgenograms revealed soft tissue swelling, and slight irregularity of the right radiocarpal joint.

Course.—The temperature continued to be 104° F. Three days after admission he developed thrombophlebitis of the left leg, with swelling and edema. There were also tenderness, spasticity, and fullness in the left flank which were thought to be due to a perinephric abscess. Excretion pyelograms revealed outward displacement of the left kidney by a markedly prominent psoas shadow; this was suggestive of a perinephric abscess. Retroperitoneal exploration revealed inflammatory adhesions and induration, with very little pus. Many fresh clots were encountered, and their removal resulted in a massive hemorrhage. Microscopic examination revealed only old and fresh blood clots containing clumps of short-chained cocci and diplococci. Despite three blood transfusions, the patient became comatose, and developed massive fatal pulmonary edema two days after operation.

Autopsy.—Autopsy revealed a normal heart which weighed 300 grams. There was bilateral bronchopneumonia, but no evidence of thrombosis or embolism. The aorta showed very slight atheromatous plaque formation throughout. Two inches above the bifurcation of the aorta there was an aneurysmal opening posteriorly, measuring 2 by 1 cm., with well-rounded edges. This led to the left into a large mass of fibrin and blood clots which infiltrated the iliopsoas, quadratus lumborum, and oblique and transversalis muscles posteriorly. This measured 6 cm. in circumference. No pus or arterial occlusion was noted. The left femoral vein below the inguinal ligament was occluded by a firm thrombus. A small thrombus was also found halfway up the

inferior vena cava. The kidneys were essentially negative except for an infarct measuring 1.5 cm. in the left renal cortex.

Microscopic examination of the aorta revealed slight atheromatous ulceration of the intima, with focal lymphocytic and fibroblastic proliferation of the intima and media. Sections through the area of rupture consisted of partly organized clot containing erythrocytes and polymorphonuclear cells, fibrin, and abundant bacterial colonies. Much necrosis was present throughout. Special elastic tissue stains revealed some splitting of the internal elastic lamina and moderate to marked thinning of the medial elastic tissue. The adventitia contained only a few scattered elastic fibers. The femoral vein contained a septic thrombus, with marked perivascular lymphocytic infiltration of the media and adventitia.

Final Diagnosis.—The final diagnosis was mycotic aneurysm of the abdominal aorta, with necrosis, rupture, and retroperitoneal hemorrhage; acute inflammatory reaction of thrombotic extravasated blood; septicemia; thrombophlebitis of the left femoral vein; bronchopneumonia; focal necrosis of the liver; and septic infarct of the left kidney.

Comment.—These cases are similar in that both occurred in young white men with a previous history of joint pains. Each entered with a chief complaint of joint pains, had a fever up to 104° F. and a leucocyte count over 20,000, with neutrophilia, and had *Str. hemolyticus* bacteriemia. No cardiac disease was found in either case, despite rheumatic histories. Septic infarctions were found in both cases, involving the kidney in one, and the kidney, lung, and spleen in the other. Both had swelling in the lumbar region which proved to be mycotic aneurysms with masses of clotted blood infected with *Str. hemolyticus*. The sequence of events in both cases was initiated by septic arthritis with septicemia. The blood stream then carried the organisms to the vasa vasorum, with resultant infectious aortitis and medial necrosis.[1] Intimal tears terminated in rupture of the mycotic aneurysms.

II. TUBERCULOSIS AND ANEURYSMS

It is the present concept that tuberculosis cannot involve the aorta unless the lungs are diseased, thereby limiting the process to the thoracic segment. Dafoe[3] found only eleven cases of aortic aneurysm due to tuberculosis, with rupture in two of the cases. He added two reports to the literature. Kornitzer[4] described a tuberculous dissecting aneurysm of the ascending aorta in a young boy with miliary tuberculosis. Schmorl[5] found five cases out of 123 autopsies on patients with acute miliary tuberculosis in which tubercle bacilli had invaded the atheromatous ulcers. The bacilli may infect the media or adventitia through the vasa vasorum. Finally, there may be direct extension from a near-by focus, such as an infected lymph node or abscess.

The process is rapidly progressive in the larger blood vessels and aorta because fibrous tissue proliferation is not so marked as in the smaller arteries, with a tendency to aneurysmal formation. The proc-

ess consists of the usual infiltration by lymphocytes and endothelial and giant cells, with caseation.

Two unusual cases are presented to illustrate the possible influence of tuberculosis as a factor in the production of saccular aneurysm of the abdominal aorta through the activity of tuberculous cold abscesses.

CASE 1.—J. F. (case of Dr. C. H. Greene), a white man, aged 50 years, was admitted with pain in the abdomen extending into the flanks and back. It was not localized, but became severe after walking. Three months previously, he suffered from pneumonia, followed by empyema.

Examination.—Examination revealed bilateral basal râles. The blood pressure was 150/90. There was tenderness in the epigastrium, and the liver extended three fingerbreaths below the costal margin. A month later he developed pains along the left leg, associated with herpetic lesions. A pulsating mass the size of an orange, with a systolic thrill and bruit, was first recognized in the abdomen. Absence of the dorsalis pedis pulsations was noted, with positive Babinski reflexes. A diagnosis was made of aneurysm of the abdominal aorta. Early gangrene of the left foot was noticed the following day. The blood pressure in the upper extremities was 140/100, but it was 70/0 in the right leg. This was thought to be due to the development of a saddle thrombus. Operation was inadvisable because of poor response to therapeutic measures. The patient failed rapidly, and died two months after admission.

Laboratory studies.—These studies included a normal electrocardiogram. Roentgenograms revealed an increase in the sweep of the second and third portions of the duodenum due to a mass or enlargement of the head of the pancreas. Both kidneys were in their normal positions. There was no evidence of paraspinal or psoas disease. Retrograde pyelograms revealed inadequate filling of the lower left renal calyces. The blood urea, creatinine, and sugar were 21, 1.1, and 84 mg. per 100 c.c., respectively. The blood Wassermann reaction was negative. The galactose tolerance test was normal. There was no free hydrochloric acid in the stomach, and the total acidity was 20 degrees. The icteric index was 19, and there was 0.55 mg. of bilirubin per 100 c.c. of serum. Repeated urinalysis revealed a trace of albumin and a few epithelial cells, erythrocytes, and leucocytes. The leucocyte count was 25,000, with 88 per cent polymorphonuclears. The temperature was normal throughout except for a terminal rise to 101° F.

Autopsy.—Autopsy revealed a glistening, blue-black discoloration of all the toes of the left foot, extending midway up the tarsus. The heart was entirely normal. The aorta presented numerous, irregularly scattered, atheromatous plaques, with an average diameter of 4 millimeters. Just below the head of the pancreas there was a fusiform sac which was fluctuant on pressure and was situated directly over the spinal column, extending 2 inches anteriorly and covering the second to the fourth lumbar vertebrae. The mass contained thick, creamy, purulent material, from which a culture was subsequently reported as positive for tubercle bacilli. Careful dissection revealed a saccular aneurysm of the abdominal aorta, measuring 2 inches in diameter. Immediately posterior to the aneurysm there was a cold abscess. Examination of the vertebrae revealed no evidence of tuberculous involvement. At the bifurcation of the inferior vena cava there was a recent

saddle thrombus extending into the iliac vessels for 3 inches. The right kidney weighed 195 grams, the left, 250 grams. The capsules were stripped with difficulty, exposing an irregular, pitted surface. The cortex was of uneven thickness, with distortion of the pyramids. On microscopic examination there was evidence of chronic pyonephritis and chronic interstitial nephritis. The aorta presented moderate atheromatous degeneration. The lungs showed bronchopneumonic consolidation, but no evidence of tuberculosis.

Final diagnosis.—The final diagnosis was saccular, arteriosclerotic aneurysm of the abdominal aorta, tuberculous cold abscess (retroperitoneal), gangrene of the left foot, saddle thrombus of the inferior vena cava, and bilateral bronchopneumonia.

CASE 2.—H. S. (case of Dr. J. H. Cawford), a white man, aged 64 years, was admitted with a history of having lost his balance after drinking, and falling on his right knee. He had had a hemorrhoidectomy three months previously. For three weeks he had had chills, fever, and a productive cough, but no dyspnea, hemoptysis, or pain in the chest. He had had occasional nausea and abdominal pain.

Examination.—Examination revealed a complete transverse fracture of the right patella. The heart was not enlarged; it was regular and there were no murmurs. The blood pressure was 144/80. The lungs showed medium moist râles and dullness at the right base posteriorly. The diagnosis was hypertensive arteriosclerotic heart disease and early bronchopneumonia.

Course.—The bronchopneumonia of the right lower lobe became more confluent and progressive, with a temperature rise to 104° F. Because of the development of a maculopapular eruption and persistence of the fever, sulfathiazole therapy was discontinued. He began to develop congestive heart failure, and digitalis therapy was instituted. His pneumonia subsided one week later, but became low grade in nature, with persistent moist râles at the bases, more marked on the right. Three weeks after admission, he suddenly developed an acute attack of dyspnea and cyanosis. Auricular fibrillation, poor heart tones, and a systolic murmur at the apex were noted. The clinical impression was pulmonary infarction. He died two hours later.

Laboratory studies.—These studies included electrocardiograms which showed complete heart block, left axis deviation, and a digitalis effect. Roentgenograms of the chest revealed bilateral bronchopneumonia, arteriosclerotic configuration of the heart, and atherosclerosis of the aortic arch. The blood culture and Wassermann reactions were negative. The blood sugar, urea, and creatinine were repeatedly normal. The leucocyte count was 10,450, with 85 per cent polynuclears. Urinalysis was slightly positive for albumin.

Autopsy.—Autopsy revealed bilateral apical adhesions, with a tuberculous cavity in the left apex measuring one inch in diameter. This contained caseous material. In the superior margin there was a single calcified nodule. The remainder of the lung showed edema and engorgement, with basal bronchopneumonia. The heart weighed 450 grams, and was the seat of coronary artery sclerosis, myocardial fibrosis, and hypertrophy of the left ventricle. The aorta was involved by numerous atheromatous plaques and hemorrhagic necrosis. One inch inferior to the right renal artery there was a saccular aneurysm 2 inches in diameter. The aneurysm was in close contact with an abscess

over the right psoas muscle. This contained 25 c.c. of light-gray, purulent material. Cultures revealed tubercle bacilli.

Microscopic examination.—This included sections of all organs, and corroborated the gross observations. Sections taken through the aneurysm revealed marked irregular intimal thickening due to hyperplastic arteriosclerosis. The media showed moderate calcification. The adventitia was uninvolved.

Final diagnosis.—The final diagnosis was saccular arteriorsclerotic aneurysm of the abdominal aorta, tuberculous cold abscess of the left apex, bilateral bronchopneumonia, arteriosclerotic and hypertensive heart disease, chronic passive congestion of all organs, and fracture of the right patella.

Comment.—These cases present certain striking similarities. They occurred in men in the fifth and sixth decades of life. There proved to be an underlying, advanced, atheromatous degeneration of the abdominal aorta. Further weakening of the wall, with aneurysm formation, probably resulted from the adjoining cold abscesses, both of which proved to be tuberculous. The fact that the masses in both cases were in the closest proximity strengthens this belief. No primary focus was recognized clinically in either case. In the first case, although the lungs and vertebrae were clear, tubercle bacilli were later demonstrated in the abscess. In the second, the focus might possibly have been the tuberculous pulmonary cavity. Another point of interest was the occurrence of gangrene of the left foot due to saddle thrombus formation. Although clinically it was placed at the bifurcation of the aorta,[2] at autopsy it proved to be at the bifurcation of the inferior vena cava.

III. MALIGNANT TUMORS AND THE AORTA

Although the aorta is susceptible to degenerative and inflammatory diseases, this highly elastic, pulsating vessel is notoriously resistant to invasion by malignant tumors. In view of their rarity and the different types of tumor involved, it was deemed worth while to report the following three cases. In the first two cases, death was caused by sudden rupture of the aorta into the esophagus; in the third case, death was precipitated by infection secondary to a reticulum cell sarcoma, with resultant saddle thrombus. Infection was a secondary factor in Cases 1 and 2, although more advanced in the latter.

CASE 1.—J. S., a white man, aged 50 years, a bricklayer, was admitted complaining of inability to swallow solid food and vomiting, accompanied by substernal pain of eight months' duration. The onset of symptoms was preceded by a cold which caused him to wheeze and spit up blood-flecked sputum on several occasions. There had been a loss of 30 pounds since the illness commenced, probably because he limited himself to a liquid diet. He had been a heavy drinker until eighteen months prior to admission.

Examination.—Examination revealed an emaciated man with wheezing respiration. The heart was in the sixth intercostal space just out-

side the midclavicular line. No murmurs were heard and the heart tones were of good quality. The blood pressure was 146/98. No metastases were found.

Laboratory studies.—These studies included an esophagram which showed a constant irregularity at the junction of the upper and middle thirds, about 2 inches in length, with slight obstruction above this point. Esophagoscopic examination revealed, at a depth of 28 cm., a fungating, easily bleeding mass, mainly on the posterior wall, but completely encircling the esophagus. It appeared to be submucosal both anteriorly and laterally, with considerable constriction. Biopsy of the esophageal mass revealed a typical epidermoid carcinoma. The blood urea, creatinine, and sugar were normal, and the Wassermann reaction was negative.

Course.—A Witzel type of gastrostomy was performed, and no metastases were found. This was done preparatory to resection of the neoplasm, with establishment of a tube graft to the upper part of the esophagus. Three weeks later, while the patient was on a bed pan, a gush of bright red blood appeared in his mouth. He fainted, and died shortly thereafter.

Autopsy.—Autopsy revealed a necrotic, ulcerated carcinoma involving the midportion of the esophagus and measuring 6 inches in length. The ulceration, about the thickness of a finger, was noted immediately beneath the posterior portion of the aorta. Opening the aorta in this region revealed two pin-point openings, surrounded by a zone of hyperemia. Pressure on the ulcerated mass caused fluid to exude into the aorta. The carcinomatous mass was firmly attached to the aortic adventitia 2 inches below the descending aorta. The aorta showed occasional, irregular, raised, subintimal, atheromatous plaques. The gastrostomy wound and the entire stomach wall were well healed. However, the stomach was distended by 1,000 c.c. of clotted blood. There was a small pulmonary abscess in the upper portion of the left lower lobe.

Microscopic examination of the esophagus confirmed the diagnosis of epidermoid carcinoma, with periesophageal necrosis and suppuration. Sections of the aorta showed the carcinoma invading the adventitia, with periaortic suppurative inflammation, necrosis, and hemorrhage. No other metastases or involvement were noted after extensive microscopic studies.

CASE 2.—P. B., a 58-year-old unemployed white man, was admitted because of bleeding from a gastrostomy wound and hematemesis which followed his supper. About eighteen months previously he had developed dysphagia, regurgitation (first solids, later liquids), and weight loss. Gastrostomy was performed at the Memorial Hospital. Three weeks earlier he had been admitted because of a similar hemorrhage. The past and family histories were noncontributory.

Examination.—Examination revealed a pale, emaciated man who was regurgitating small amounts of bright red blood. Blood was exuding from the opening in the left side of the epigastrium. There were no lymph node enlargements or metastases. The blood pressure was 86/60, and the heart, lung, and abdominal examination was negative. He continued to bleed profusely and died twenty hours after admission.

Autopsy.—Autopsy revealed an epidermoid carcinoma of the esophagus which had eroded into the aorta at the level of the tracheal bifurcation. Death resulted from a split-pea-sized rupture of the aorta,

rather than bleeding from the malignancy itself. The carcinoma did not invade the trachea or regional lymph nodes, but was firmly attached to the adventitia of the adjacent aorta.

CASE 3.—H. T. (case of Dr. B. Fedde), a white female houseworker, aged 39 years, was admitted with a history of pain of a girdle nature around the abdomen and in the lower extremities. There was also weakness of the legs. She was irrational and confused.

Examination.—Examination revealed paralysis of both lower extremities, with flaccidity and bilateral foot drop. All reflexes and sensations were absent in the legs. There were muscle tenderness and pain on passive motion of the legs. The right leg was very cold below the knee, and the left was cold below midleg. Later this extended to about mid-thigh in an irregular manner. The dorsalis pedis artery pulsations were not palpable. Neurosurgical consultation by Dr. J. Browder, three days later, led to a diagnosis of occlusion of the abdominal aorta at the iliac bifurcation, but it was then too late to intervene. The patient died six days later because of the increasing extent of the gangrene.

Laboratory studies.—These studies revealed a normal spinal fluid, no nitrogen retention in the blood, and a negative Wassermann reaction. The leucocyte count rose from 38,900 to 66,300 (with 81 per cent polynuclears)·in three days. Roentgenologic examination suggested the presence of a left iliopsoas mass. The temperature ranged from 98° to 99.8° F.

Autopsy.—The heart weighed 520 grams and contained no thrombi or vegetations. Situated at the bifurcation of the aorta was a saddle thrombus extending 1¼ inches upward into the aorta, 2 inches into the right common iliac artery, and 1 inch into the left common iliac artery; both iliac arteries were completely occluded. The thrombus was well organized, gray white, and very adherent to the intima. There was a bilateral abscess over the lower fourth of the psoas muscles. A small tumor overlying the fifth lumbar vertebra proved to be a reticulum cell sarcoma which invaded this vertebra, with secondary abscess formation. Other sections of the aorta showed myxomatous degeneration of the intima and media, with organizing adherent thrombi. In the periaortic tissues there was septic thrombosis of the capillaries.

Comment.—The sequence of events in this case began with a small, reticulum-cell sarcoma which invaded the area about the fifth lumbar vertebra in close proximity to the aorta. Resultant infection, with the formation of bilateral psoas abscesses, produced the additional factors of infection and pressure upon the aorta. However, before the process could invade far enough to produce actual rupture, a saddle thrombus formed[2] and caused complete occlusion.

SUMMARY

1. Two strikingly similar cases of mycotic aneurysm of the abdominal aorta, with rupture, are reported. The primary focus in both was septic arthritis caused by the *Str. hemolyticus.* The diagnosis was made ante mortem in one of the cases.

2. Two rare cases of saccular aneurysms of the abdominal aorta, due to atheromatous degeneration in association with tuberculous cold abscesses, are presented.

3. Three cases of malignant tumor of contiguous structures affecting the aorta are described. In two similar cases, the process was an epidermoid carcinoma of the esophagus; in the third, it was a reticulum-cell sarcoma. Secondary infection occurred in both cases and was the immediate cause of death in the third case.

I am indebted to Dr. William Hala and Dr. C. Burn for the pathologic studies.

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EFFECTS OF EMETINE ON THE ELECTROCARDIOGRAM

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EMETINE hydrochloride has been used in the treatment of amoebic dysentery since Rogers[1, 2] advocated it in 1912. Levy and Rowntree,[3] in 1916, called attention to the dangerous effects of large amounts of emetine on the circulatory system, and supported their contention with experimental animal work. Goetz[4] reported on the therapeutic effects and dangers of emetine at the Medical Association of the Isthmian Canal Zone in 1936. Since that time the electrocardiograph has been used at the Gorgas Hospital to aid in the evaluation of the condition of the heart while the patient is under emetine therapy. Recently, Boyd and Scherf[5] used experimental animals to study the effects of acute emetine intoxication. They found, among other changes, widening of the ventricular complex, which was accompanied by cardiac dilatation. Auriculoventricular conduction time changes were noted. They found that the T wave tended to assume a reciprocal relationship to the initial deflection. Auricular extrasystoles and auricular tachycardias were the most common arrhythmias. Advanced stages of intoxication were required for the production of ventricular extrasystoles. Chopra and Sen[6] reported S-T depression in a case of emetine intoxication, although Boyd and Scherf did not think that this was due to emetine.

We have reviewed a number of the charts of patients who received emetine treatment for amoebic dysentery at the Gorgas Hospital. Those who were ill with other diseases which might affect the electrocardiogram were eliminated. This series is composed of seventy-two cases, in all of which electrocardiograms were taken before, during, and at the end of the emetine treatment. A number of the patients had additional records which were taken during or after the therapeutic course. The routine therapy consisted of one-half grain of emetine hydrochloride subcutaneously twice a day for ten days. Emetine by mouth was not used in this study.

Changes were noted in all limb leads equally, and were less common in Lead IVF. Q-wave changes were not found. Thirty-eight, or 52.7 per cent of the series, showed changes. Thirty-three of these, or 45.8 per cent of the total of seventy-two, had depression of the T waves varying from slight lowering of the amplitude to complete inversion. Ten of these showed inversion in one or more leads. The auriculoventricular conduction time was increased in seven instances (9.7 per cent), but in only one case did it become abnormal. This

occurred on the seventh day of the ten-day course; the P-R interval was lengthened to 0.24 second, i.e., first degree A-V heart block. The condition persisted through the tenth day, and then decreased slowly until, on the eighteenth day, the conduction time was 0.20 second (Fig. 1). Only four in the group (5.5 per cent) showed premature systoles. These were both auricular and ventricular, but the ventricular premature systoles predominated. Only one patient had auricular premature systoles and these changed to ventricular with added amounts of emetine. A coronary T wave occurred in one case, and is described in detail.

Before emetine · · · · · · · · · · · 7th day · · · · · · · · · · · 18th day
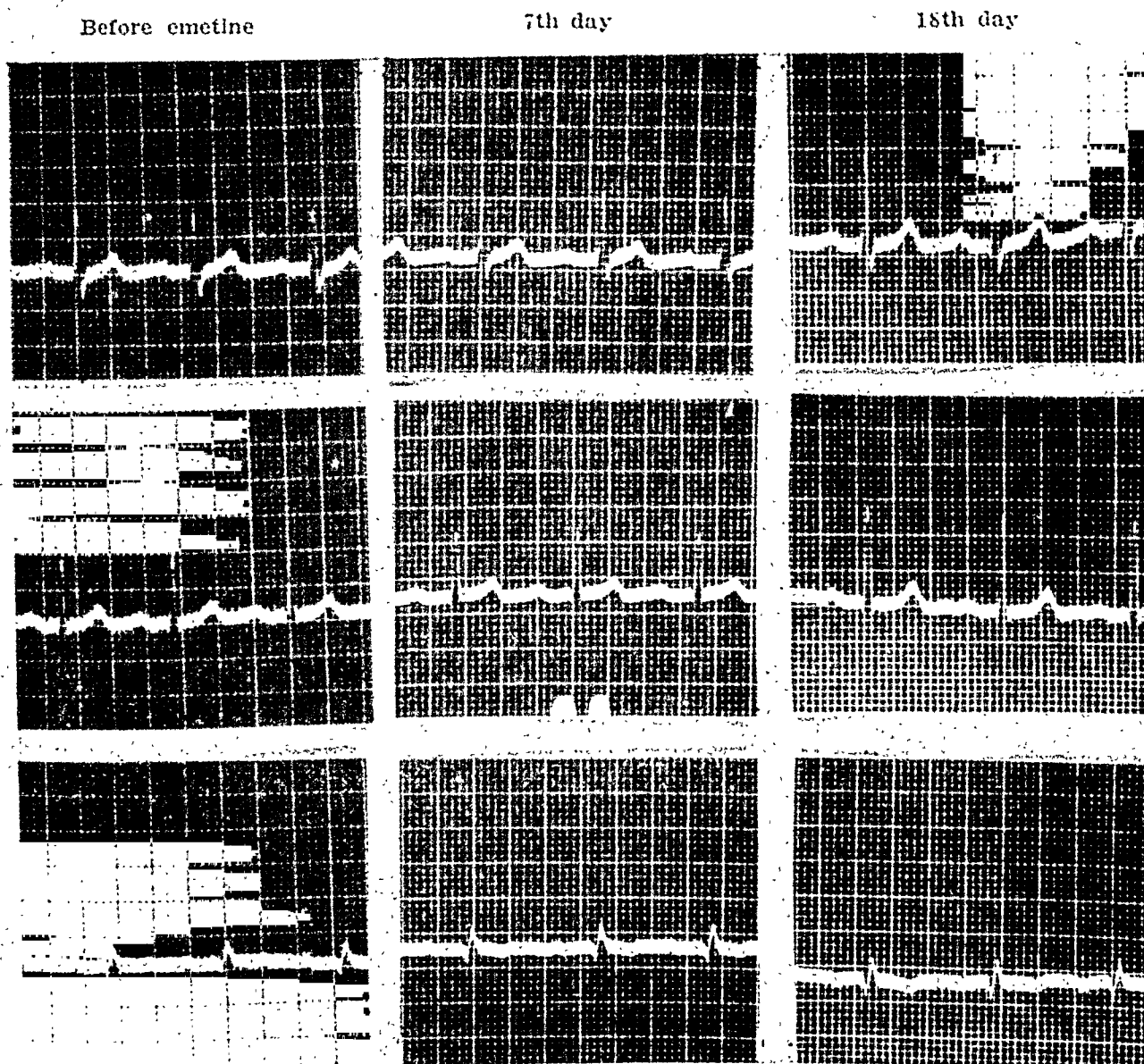
Fig. 1.—The above electrocardiogram shows increased auriculoventricular conduction time following emetine. This was first noted on the seventh day of treatment and persisted through the tenth day, when the drug was discontinued. This was followed by slow return toward normal.

REPORT OF CASES

CASE 1.—In the case of F. R., a native of Costa Rica, 31 years of age, changes in the electrocardiogram were brought about by emetine. These changes were not permanent, but were more than transitory, for they persisted over a period of at least four weeks after the drug had been discontinued (Fig. 2).

He entered the hospital Aug. 28, 1942. Emetine therapy was instituted September 3, and continued for ten days in doses of one-half grain twice a day. An electrocardiogram taken before therapy was normal. Successive tracings were made at intervals until the thirty-fifth day. The only significant changes were in the amplitude of the T waves, as shown in Table I.

Before emetine	16th day	6th month
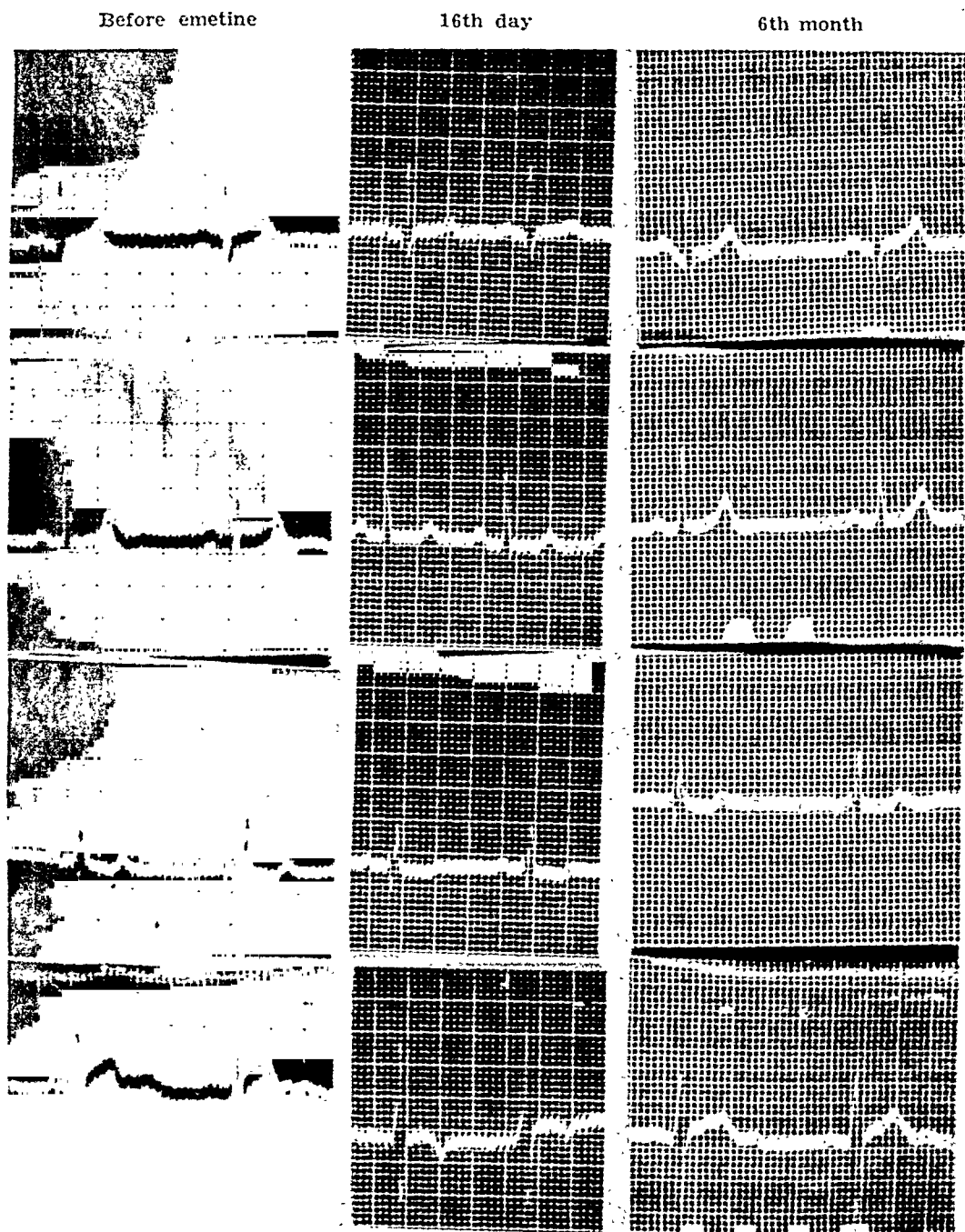
Fig. 2.—Representative electrocardiograms showing the lowering of T waves in the limb leads and inversion of T₄. Followed much later by return to normal (Case 1).

The patient complained of precordial pain on the last day of treatment, when T₄ first showed changes. This pain would come on during rest in bed, and was not severe. It would persist for about an hour.

The sharp feature of the pain continued for ten days, and was then followed by a precordial ache which disappeared after two more weeks.

The probability of myocardial infarction was given consideration in view of the precordial pain and coronary type of T wave in Lead IV. However, there were no changes in the RS-T segments, R_4 persisted, and no Q-wave changes were present. Also, there was no temperature elevation or leucocytosis, and the sedimentation rate remained normal. No friction rub was heard.

The patient was permitted to return to work October 17; he was asymptomatic, but T_4 was still inverted. Instructions were given to report for a recheck in one month, but he did not do this. He was not seen again until March, 1943, when he returned for another cause. The electrocardiogram was normal, with an upright T_4 of 4 millimeters.

Emetine was given subcutaneously to four other patients to note the immediate effect. Electrocardiograms were taken at intervals of five minutes and one-half hour after emetine hydrochloride was injected.

TABLE I

DAY OF MEDICATION	AMPLITUDE OF T WAVES (MM.)				MISCELLANEOUS
	T_1	T_2	T_3	T_4	
0	2.50	3.50	1.50	3	Before emetine
5	2	2.50	1	3	Upright T_4
10	2	1.50	−1.50	Diphasic +2 and −1.50	Last day of medication Onset of pain
16	1	1.50	−0.50	−2	Post emetine
19	0.50	1.50	0.75	−2.50	
23	0.50	1.50	1	−3	
28	1	2	1	−2.50	
35	0.75	2	1	−2.50	Inverted T_4
6 mo.	3.1	4.2	1	4	Upright T_4

TABLE II

TIME OF MEDICATION	SECONDS A-V INTERVAL	AMPLITUDE OF T WAVES (MM.)				MISCELLANEOUS
		T_1	T_2	T_3	T_4	
0	0.16	1	1.25	0.25	2	Left axis deviation R_4 present
5th day before medication	0.16	0.75	0.50	Slight inversion	0.75	R_4 absent Auricular extrasystoles
5 min. after medication	0.17	0.50	Diphasic +0.25 and −0.50	Slight inversion	0.25	Ventricular extrasystoles Marked sinus arrhythmia
½ hr. after medication	0.17	0.50	Diphasic +0.50 and −0.50	Slight inversion	−0.25	Ventricular extrasystoles

CASE 2.—This experiment was on a 69-year-old Negro who had been receiving emetine for five days. Slight T-wave changes were pre-

sent. Further, slight T-wave depressions occurred, and marked sinus arrhythmia was present immediately after the injection of one-half grain of emetine. This was noted neither before the injection nor one-half hour later. Reference to Table II will show the degree of changes.

Boyd and Scherf[5] produced premature auricular and ventricular systoles experimentally in animals, and believe that the ventricular extrasystoles occur with advanced intoxication. Here the auricular extrasystoles disappeared, and ventricular extra beats appeared as an immediate effect after the injection of emetine. It is of interest that R_4 disappeared during the first five days of treatment.

CASE 3.—Another study was made on an East Indian, 60 years of age, who had received no emetine previously. Here we noted an immediate effect from one grain of emetine. The patient later received ½ grain twice a day for eight days. It was discontinued because of diarrhea which was thought to be due to the drug. The only changes of interest in the record occurred in Lead IV. T_4, which was inverted before the injection of the drug, became positive one-half hour after its administration. This may have been due to the reciprocal action on the T waves described by Boyd and Scherf. The position of the electrode over the precordium was the same for each tracing. R_4, which was less than 1 mm. before injection of the drug, became very high. Table III shows the changes as they occurred.

TABLE III

TIME OF MEDICATION	AMPLITUDE OF T WAVES (MM.)				QRS$_4$		MISCELLANEOUS
	T_1	T_2	T_3	T_4	R_4	S_4	
0	2	3	1.50	−1.50	Very small	Very small	
5 min. after medication	2.50	3	1.50	−1	7	−3	
½ hr. after medication	2	3	1.50	3.50	23	−2	
6th day	2	3	1	−0.50	8	−2	
10th day	2	2	Isoelectric	3	13	−4	Left axis deviation

TABLE IV

TIME OF MEDICATION	SECONDS	AMPLITUDE OF T WAVES (MM.)			
	A-V INTERVAL	T_1	T_2	T_3	T_4
0	0.16	2.50	3.50	0.75	6.50
5 min. after medication	0.17	2	2.50	0.25	4.50
½ hr. after medication	0.18	1.50	1.75	0.25	4.50
5th day	0.18	1.50	2	0.50	2.50

CASE 4.—This was a Latin-American Negro, 30 years of age. Electrocardiograms were made immediately, as in other cases, after an initial dose of one-half grain of emetine subcutaneously. There were slight lowering of the T waves and lengthening of the P-R interval.

CASE 5.—The last case was that of a Latin-American Negro, 27 years of age. He received one-half grain of emetine on the first day, after which the electrocardiograms shown in Table V were taken. One-half

TABLE V

TIME OF MEDICATION	SECONDS	AMPLITUDE OF T WAVES (MM.)			
	A-V INTERVAL	T_1	T_2	T_3	T_4
0	0.16	1.50	3	2	1.50
5 min. after medication	0.16	1.50	3	2	1
½ hr. after medication	0.16	1	2.50	2	1.25
5 min. after second medication	0.16	0.75	2.50	1.50	+0.75 −0.25
½ hr. after second medication	0.16	1	3	1.50	1.50

hour after the first injection, another one-half grain was given, and electrocardiograms were taken again in five minutes and one-half hour. Minor T-wave changes occurred.

DISCUSSION

We have had no unfortunate experiences with emetine hydrochloride as used. Occasionally, when the electrocardiogram shows marked changes, it is best to discontinue medication before the full course is given. Carbarsone has also been used with emetine in some cases, but these patients did not show additional electrocardiographic changes. For the most part, the changes noted are of minor and temporary nature. Most of the patients have had little or no diarrhea during the treatment, but all received supplementary vitamins. The observations in Case 1 make it necessary to consider more severe myocardial effects of the drug. It is possible that mild myocardial infarction occurred in this case. No emetine deaths have occurred at Gorgas Hospital.

CONCLUSIONS

1. Emetine produces minor changes in the electrocardiogram, consisting, for the most part, of T-wave depressions in all leads. These changes are most frequently noted in the limb leads, and are temporary in nature.

2. Emetine hydrochloride, as used in the present study, does not seem to be dangerous, although electrocardiographic studies should be made before and during treatment.

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INCREASED CAPILLARY FRAGILITY IN HYPERTENSION: INCIDENCE, COMPLICATIONS, AND TREATMENT

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IN 1940, Paterson[1] stated: "capillary rupture with intimal hemorrhage in relation to the precipitation of coronary thrombi has been described. . . ." by Paterson,[2] Wartman,[3] and Winternitz and his co-workers.[4] He goes on to state: "capillary rupture with intimal hemorrhage is intimately concerned with the mechanism of cerebral arterial thrombosis and possibly, in certain cases, with the causation of cerebral arteriospasm and rupture. It is suggested that the factors responsible for the rupture of intimal capillaries in the cerebral arteries are high intracapillary pressure from hypertension, progressive atheromatous degeneration of the supporting tissue and increased capillary fragility from a variety of causes."

It seemed possible, therefore, that an abnormal condition of the capillaries might be a factor in the production of certain of the vascular accidents which sometimes occur in cases of hypertension. We were especially interested in the relation of such complications to thiocyanate therapy, for we had noted cutaneous ecchymoses rather commonly, retinal hemorrhages less commonly, and apoplexy and coronary occlusion very rarely after the initiation of such therapy. The more serious complications were rare enough to suggest that they were merely coincidental, yet were regarded as alarming nevertheless.

METHOD AND MATERIAL

For a period of eighteen months all persons with hypertension who were routinely studied in our laboratory had, in addition, a measurement of capillary fragility by the Petechial Index of Göthlin,[5] with certain minor modifications.

Technique of the Test.—(1) Mark off a circular area, 6 cm. in diameter, in each antecubital area. Mark off all blemishes and marks in this area that might later be confused with petechiae. (2) Place a standard blood pressure cuff about each arm, and maintain in each a pressure of 35 mm. of mercury for fifteen minutes. Lower the pressure, and count and mark all petechiae within the two circular areas, using a good light and a magnifying lens of 5 D or its equivalent. (3) One hour or more later, repeat, using a cuff pressure of 50 mm. of mercury.

The Petechial Index is calculated as follows: To the number of petechiae occurring at 35 mm. of mercury multiplied by 2, add the additional number occurring at 50 millimeters. Based upon the

Petechial Index, capillary fragility is considered to be: (a) normal, if the Index is 8 or less, (b) increased (abnormal) if the Index is 13 or more, and (c) borderline, but probably abnormal, if the Index is 9 to 12.

In order to save time, the second stage can be omitted under the following conditions: (1) The number of petechiae after the first stage is 2 or less. Such persons may be considered normal. Usually, but not invariably, the person is normal who has 3 petechiae after the first stage. (2) If 6 or more petechiae appear after the first stage, the subject may be considered abnormal. (3) The test is a repetition, and may be compared with the corresponding first stage of an earlier test. Repetition in less than three weeks, however, is unreliable in any case.

The second stage should always be done if the fragility is being tested in a subject for the first time and there are 4 or 5 petechiae after the first stage. It should also be done in most cases when the number after the first stage is 3.

The patients, 265 in all, had history and physical examination by various members of our hospital staff and referring physicians. Special attention was paid to the following: (1) history suggesting apoplexy, (2) history of spontaneous cutaneous ecchymoses, (3) presence of retinal hemorrhages, as ascertained by ophthalmoscopic examination, and (4) simultaneous medication with thiocyanate.

Ophthalmoscopic examination was carried out by physicians with varying degrees of skill, so that the occurrence of retinal hemorrhages as a positive sign may be accepted, whereas their absence did not necessarily entirely exclude them.

The period of study was never less than six months nor more than twenty months.

Thirty-three patients with increased fragility were treated with Hesperidin* by mouth in a dose of 250 to 500 mg. three times a day, and nine more were given Hesperidin Methyl Chalcone* by mouth in a dose of 10 mg. three times a day. In addition, fourteen such patients were treated with Rutin, the result of which has already been reported.[6]

RESULTS

1. Incidence of increased capillary fragility: As shown in Fig. 1, capillary fragility was found to be normal in 218 of the series, or 82 per cent (approximately). It was definitely increased in 44 subjects, whereas, in three, it was borderline, making a total of 47 persons, or 18 per cent (approximately), whose capillary fragility was, at least, not normal. Judging from the occurrence of complications, it appears that the borderline group should be classed as definitely abnormal.

2. Relation of capillary fragility to sex and age: As shown in Fig. 1, there was no significant relationship between capillary fragility and either sex or age.

3. Relation of capillary fragility to blood pressure level: Fig. 2 shows the systolic and diastolic blood pressure of 54 patients with increased capillary fragility. There was obviously no relationship between the occurrence of increased capillary fragility and blood pressure level. This series of 54 patients was obtained by adding to the

*Supplied by Abbott Laboratories, North Chicago, Ill.

original series of 47, seven subjects from an earlier group who were called back for study because they had developed one or more of the "complications" of increased fragility.

4. Relation of capillary fragility to the occurrence of apoplexy: A history of apoplexy, followed by paralysis, was obtained in four cases, or 2 per cent (approximately) of the patients whose capillary fragility was normal. Four more subjects in this group gave an atypical history, namely, that a diagnosis of apoplexy had at one time been made (usually a severe headache was described as a "slight stroke"), but there never was any paralysis, nor were there any neurological sequelae at the time the patient was studied. If these were included, it would raise the incidence of apoplexy in the group with normal fragility to 4 per cent. On the other hand, seven of the patients with increased fragility gave a definite history of apoplexy followed by paralysis, and five more had strokes during the period of observation, making a total incidence in the group of twelve, or 25 per cent (approximately). It would appear, therefore, that apoplexy occurred with greater frequency in persons with hypertension associated with increased fragility than in those with normal capillary fragility.

5. Relation of capillary fragility to the occurrence of retinal hemorrhages: Retinal hemorrhages were recognized in five persons with normal capillary fragility, or 2 per cent (approximately), and in ten persons, or 21 per cent (approximately), whose capillary fragility was increased. It seems likely, therefore, that retinal hemorrhages occur more commonly in those persons with hypertension whose capillary fragility is increased.

6. Relation of capillary fragility to thiocyanate medication: Ten persons were studied who were attending our dispensary and receiving thiocyanate prior to the beginning of this investigation. These persons were chosen because all of them showed either cutaneous ecchymoses (nine cases) or retinal hemorrhages (one case) beginning soon after the onset of thiocyanate medication. All ten persons showed an increase in capillary fragility. Three other patients with increased capillary fragility were given thiocyanate without other treatment. One patient developed cutaneous ecchymoses, one developed retinal hemorrhages, and the third died of a stroke. We have not felt justified in continuing this phase of the study, but have made it a rule never to give thiocyanate to a patient with increased capillary fragility until, or unless, that fragility has become normal as the result of treatment. Thiocyanate therapy has been used in twelve such cases without incident.

7. Relation of capillary fragility to mortality: During the twenty months' period of study there were three deaths in the group with normal fragility, or 1 per cent (approximately), and five deaths, or 10 per cent (approximately), in the group with increased fragility. It seems probable that the mortality is greater among persons with

hypertension and increased capillary fragility than among those with hypertension and normal fragility.

8. Effect of treatment: Hesperidin was given to 33 persons with increased capillary fragility, only 23 of whom were adequately fol-

CAPILLARY FRAGILITY
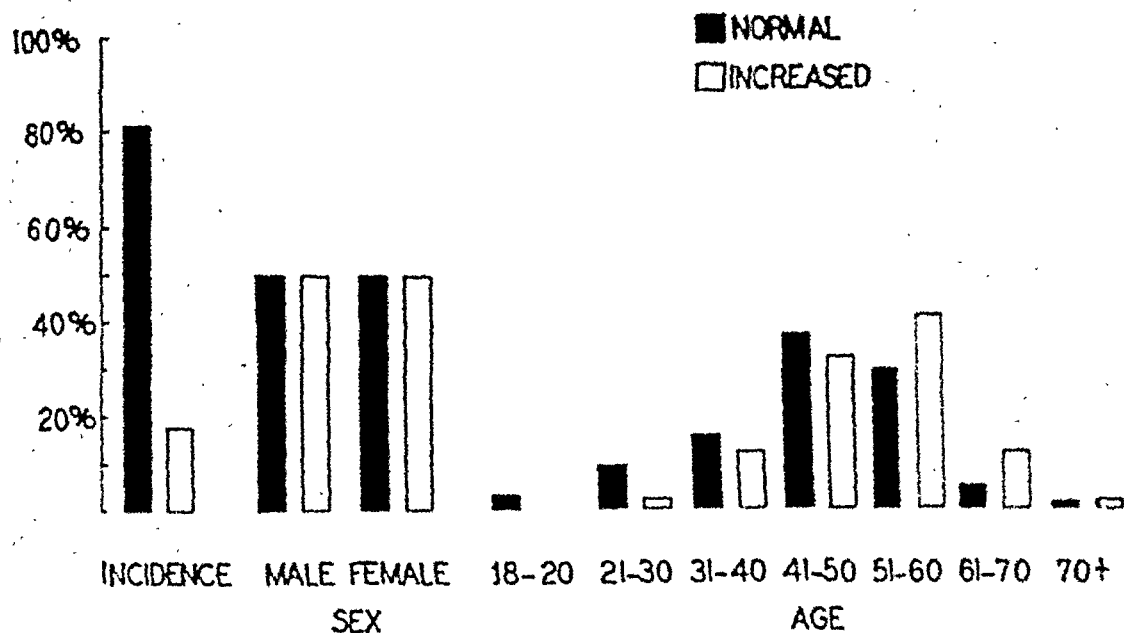
Fig. 1.—Chart comparing the incidence of normal and increased capillary fragility in the general hypertensive group (on the left) and in groups selected on the basis of sex and age. The figures for the two columns on the left are expressed as percentage of the entire group of 265 cases. The percentage figures for sex and age, however, refer only to the total group with normal fragility (filled-in rectangle) or increased fragility (open rectangle). The age is expressed in years.
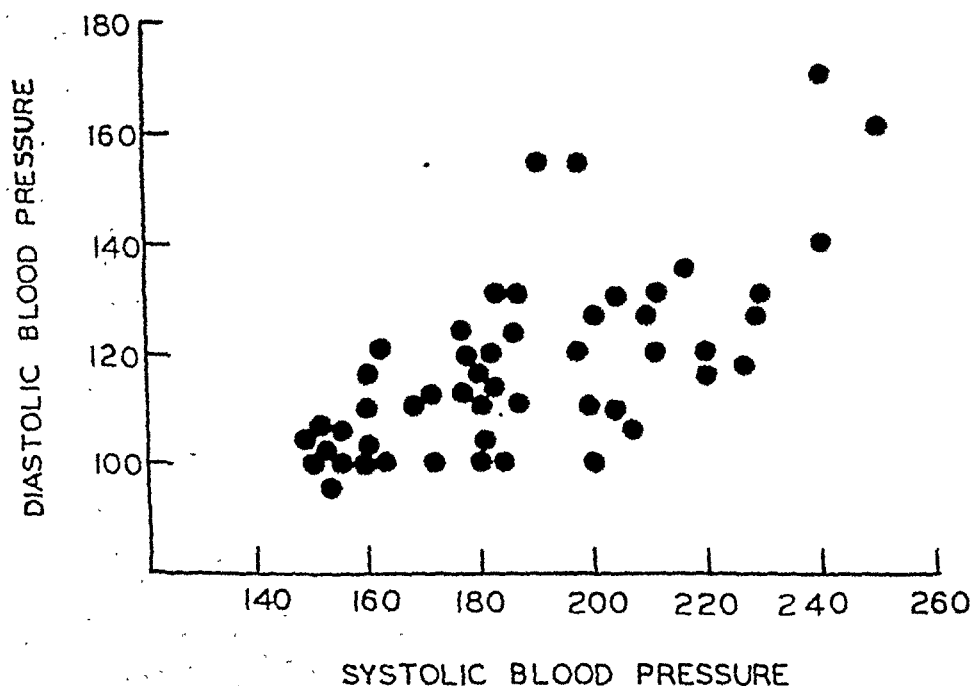
Fig. 2.—Chart showing the systolic and diastolic blood pressure of 54 persons with increased capillary fragility. Each dot represents one subject.

lowed. In 20 of these, capillary fragility, as measured by Göthlin's test, became normal within one or two months after starting treatment, and remained so thereafter except in two instances, in which the pa-

tient discontinued treatment without permission, when the test became abnormal, to become normal again when treatment was resumed. In three subjects the capillary fragility was not affected by treatment and remained abnormal; two of these developed apoplexy and died. One of the 20 patients whose fragility returned to normal after therapy also died of apoplexy. This patient had a high degree of papilledema when first seen.

Hesperidin methyl chalcone was given to nine persons with increased capillary fragility. In seven of these the fragility became normal, while two were unaffected. This group has been followed only six to nine months, and no complications have occurred in any of the nine subjects.

We have not felt justified in discontinuing medication at intervals to secure adequate controls for its effectiveness. Also, one cannot say with the evidence at hand that reversion of Göthlin's test to normal indicates that the subject is less likely to suffer one of the hemorrhagic complications of hypertension, but it seems likely that such is the case.

SUMMARY

1 Capillary fragility was increased in about 18 per cent of 265 cases of hypertension. This incidence was not related to sex, age, or degree of hypertension.

2. Persons with increased capillary fragility are especially predisposed to apoplexy, retinal hemorrhage, and death.

3. Thiocyanate tends to make worse a previously abnormal fragility, or perhaps in certain cases may even change fragility from normal to increased. When this occurs, thiocyanate may be a factor in the causation of apoplexy and other hemorrhagic phenomena.

4. Hesperidin and hesperidin methyl chalcone restored fragility to normal in about 84 per cent of cases of increased capillary fragility. It is hoped, but not yet proved, that this may also lessen the frequency of the complications of increased capillary fragility.

5. It is probable that thiocyanate should not be given to persons with increased capillary fragility, unless or until that fragility has become normal as the result of therapy. After this has been done, thiocyanate apparently can be given with impunity.

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BLOOD PRESSURE IN THE ARM AND THIGH OF MAN

I. A Study of Averages, Variations, and Differences Between Thigh and Arm

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THE blood pressure in the extremities of man has been of interest ever since blood pressure could be measured clinically, yet many questions relative to it remain unanswered. For example, there have been assertions and denials that the blood pressure in the legs of the recumbent subject is higher than that in the arms. Those who believe it is do not agree on the explanation of this physiologic curiosity. Many physicians forget that variations of blood pressure occur in so-called normal persons, and the attempt to ascertain "normal" responses as a result of study of small groups of subjects has been invalidated in some degree by the variability. The value of studies limited to the influence of a single factor, such as posture, for example, is limited because factors other than posture are not considered at the same time. It is easy to err in conclusions relative to the physiology of the circulation by noting the changes of pulse rate in one group of subjects, the reactions of blood pressure in another group of subjects, studied perhaps under entirely different experimental conditions, and the effects of exercise on a third group of subjects under still different circumstances. The present studies were on the influence of several factors on blood pressure in the same group of patients.[*]

HISTORICAL ASPECTS

Since 1908, numerous investigators[1-18] have studied blood pressure in the four extremities. Prior to 1924, it was generally felt that the blood pressure in the legs was not higher than that in the arms of normal subjects, provided the hydrostatic effect (head higher than the feet) was excluded. In 1924, Bazett,[1] by direct methods, noted in dogs a higher systolic pressure in the brachial than in the carotid artery. The systolic pressure in the femoral was higher than that in the brachial artery, but the diastolic pressure was the same throughout the arterial tree. He hypothesized a possible mechanism for such differences of pressure, which involves the transformation of the greater kinetic energy in the legs into stress or pressure energy. Burdick and his associates,[2] who studied four normal subjects by a photographic technique, concluded that the blood pressure in the thighs of resting subjects in the horizontal posture was 38 mm. higher than in the arms. This figure increased to 67 mm. with exercise. In 1929,

Strang,[16] after a careful study of fifty-four normal people, concluded that the blood pressure in the legs is higher than that in the arms, regardless of the position of the body; the average difference was 33 mm. of mercury. Hamilton and his associates[7] studies of blood pressure, in 1936, by direct arterial punctures on thirty human subjects left no doubt that the blood pressure is higher in the legs than in the arms, even when subjects are in the horizontal posture. Cady[3] consistently found a higher systolic pressure in the popliteal than in the brachial artery. The difference was greatest in hypertensive subjects and in those who received drugs causing arteriolar constriction. After lumbar sympathectomy and after the use of drugs which caused arteriolar relaxation, it was smaller. In dogs the blood pressure measured by arterial puncture was higher in the femoral than in the carotid artery.

PROCEDURES

The 112 unselected subjects of this study* had a wide variety of clinical states, many of which were not organic. With the exception of two cases of essential hypertension, the subjects did not have any significant vascular disease. Sixty-nine of the subjects were male and forty-three were female. Their ages ranged from 12 to 65 years; the average was 39.7 years. During the course of all the studies, including those which are to be reported in subsequent papers, 2,415 measurements of blood pressure and 635 counts of the pulse rate were recorded. Subjects sat on the examining table for one to two hours, during which time a neurological history and examination were carried out. At the close of the examination, the subject lay on the table with the arms and legs in the horizontal position. A Tycos aneroid sphygmomanometer† cuff which was 5½ inches (14 cm.) wide was then placed around the left arm, and a leather-covered pneumatic cuff, 5 inches (12.7 cm.) in width, held in place by straps and buckles, was placed around each thigh just above the knee. The point at which the first Korotkoff sound was heard was accepted as the systolic blood pressure, and that point at which the sounds were suddenly muffled was taken as the diastolic pressure. In most instances, this latter point was definite. After subjects had been in the horizontal posture for about five minutes, blood pressure readings in the left arm, right thigh, and left thigh were taken in that order, after counting the pulse rate. After two minutes, a second series of blood pressures and pulse rates was recorded. In most instances, the left thigh cuff was rapidly inflated to a point greater than the estimated systolic blood pressure in the standing posture. The subject then assumed the standing posture and remained quiet. At the end of one minute in that position the pulse rate was counted, after which the blood pressure was measured in the right thigh. The cuff around the left thigh was then deflated, during which process the blood pressure was measured. Two minutes later, in a second series of studies, the blood pressure was measured in the left arm, right thigh, and left thigh, in that order,

and the pulse rate was counted. The subject then assumed the supine position. An identical series of studies was made at the end of one minute and again at the end of three minutes in this posture.

CRITICISMS

Obviously, the methods which were employed in this study are subject to some criticism. We are fully aware of the lack of precision and control, which might in part be obviated were one working with trained animals under laboratory conditions. However, it is felt that the conditions of study were sufficiently accurate to denote trends, and, above all, to demonstrate the marked variability of vascular response which may occur in the same person and among different persons. If this study does nothing more than emphasize the importance of biologic variability, it will have been worth while.

That estimation of the diastolic pressure is subject to more error than is that of the systolic is widely appreciated. This is especially true when congestion of the leg caused by standing or by slow deflation of the pressure cuff renders the diastolic sound feeble and poorly demarcated.

The old question arises as to the accuracy of indirect measurement of blood pressure. Although this method is not as accurate as the direct one, Hamilton and his associates[7] have stated, as a result of intra-arterial measurements of blood pressure in man, that the indirect method is accurate enough for most purposes.

Simultaneous measurement of blood pressure in the arm and leg was not possible. That this might lead to errors in interpretation is well appreciated. However, the magnitude and direction of the observed changes were so great and consistent as to leave little doubt of their significance. Strang[16] studied the blood pressure in the arm just before and just after measuring the blood pressure in the thigh, but did not note any significant differences between readings made under those circumstances.

In some respects, it might have been desirable to tilt subjects passively to the upright posture, but this was not feasible. Strang found that the effect of tonic contraction of muscles incident to standing was rather small, but was greater in the leg than in the arm.

The question arises as to whether a 5-inch cuff (12.7 cm.) is wide enough for measuring accurately the blood pressure in the thigh of an obese person. Erlanger and Hooker[19] stated that if the artery is compressed as much as 4 cm. the cuff is adequate. Wiggers[20] has stated that a cuff which is 13 cm. in width is ample. The cuffs which we used largely satisfied this criterion, and were constructed in such a way as to prevent any ballooning about the margins of the cuff. They were, of course, a source of some discomfort. Wider cuffs would have added to the discomfort, probably without increasing the accuracy of the readings.

RESULTS

The average values for the blood pressure, for pulse pressure, for difference of blood pressure between the arm and the thigh, and for pulse rate in both postures in 112 cases are to be found in Fig. 1 (derived from Table I). The systolic pressure in the arm remained unchanged, but the systolic and diastolic pressure in the thigh, the systolic and diastolic differential in pressure between thigh and arm, and the pulse rate increased on standing. The pulse pressure decreased in the arm and thigh, but to a greater extent in the arm, mainly because the systolic pressure failed to increase along with the diastolic pressure on standing. For the same reason, there was a greater increase in systolic than in diastolic thigh-arm differential* pressure.

TABLE I

MAXIMAL, MINIMAL, AND AVERAGE VALUES FOR THE SYSTOLIC AND DIASTOLIC BLOOD
PRESSURE AND PULSE PRESSURE IN THE ARM AND THIGH, DIFFERENTIAL
PRESSURE (MILLIMETERS OF MERCURY), AND PULSE RATE.
HORIZONTAL AND STANDING POSTURE. 112 CASES

PRESSURE		HORIZONTAL			STANDING		
		MAX.	MIN.	AV.	MAX.	MIN.	AV.
Arm.	Systolic	234	94	115	244	80	115
	Diastolic	144	56	77	144	54	83
	Pulse pressure	90	16	38	100	8	32
Thigh	Systolic	296	100	150	310	100	193
	Diastolic	188	42	104	258	76	149
	Pulse pressure	104	14	46	76	10	44
Differential blood pressure	Systolic	64	−4	35	128	−4	78
	Diastolic	60	−20	27	104	2	66
Pulse rate		100	48	75	124	56	94

TABLE II .

DIRECTION AND AVERAGE DEGREE OF CHANGE (IN MILLIMETERS OF MERCURY)
OF ARM AND THIGH PRESSURES IN SUCCESSIVE READINGS AT ONE
AND THREE MINUTES IN EACH POSTURE. 112 CASES

PRESSURE	POSTURE	ARM		THIGH	
		1 MIN.	3 MIN.	1 MIN.	3 MIN.
Systolic	Lying		−3		+ 3
	Standing	+1	−1	+43	+43
Diastolic	Lying		−1		+14
	Standing	+6	+6	+37.	+45

The failure of the systolic pressure in the arm to rise while the diastolic pressure in the arm increased an average of 6 mm. on standing is in general keeping with the observations of many observers,[21-27] who have found that the diastolic pressure in the arm rises an average of 10 to 12 mm. while the systolic pressure in the arm may rise, remain stationary, or decrease with assumption of the standing posture. The systolic pressure in the thigh did not change materially on successive readings (Table II). This was also true for the diastolic pressure in

*Hereafter, for the sake of brevity, the term "differential" will denote the difference between the blood pressure in the thigh and that in the arm. Normally, blood pressure in the thigh is higher than in the arm.

the arm, but, in the thigh, the second diastolic reading, while the subject was horizontal, was, on the average, 14 mm. higher than the first. In the standing posture, the second diastolic reading averaged 8 mm. higher than the first.

The extent of variation of blood pressure from the average for the group is indicated in Table III. Thus, only 59.5 per cent of all the blood pressures fell within 10 per cent of the average, whereas 86.5 per cent of the readings fell within 20 per cent of the group average.
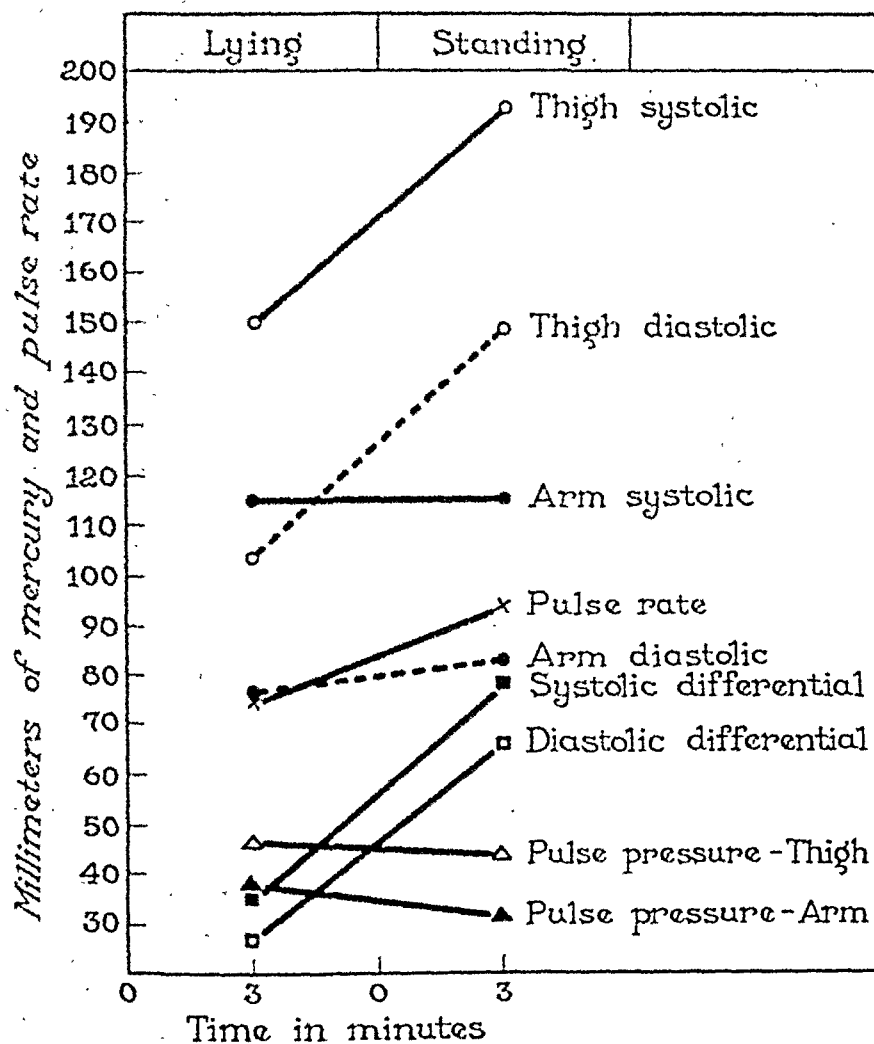
Fig. 1.—Average values for systolic and diastolic blood pressure and pulse pressure in the arm and thigh, differential blood pressure, and pulse rate of 112 subjects in horizontal and upright postures.

These results are almost identical with those of Strang, who found in a careful study of fifty-four normal subjects that 60 per cent of the blood pressure readings fell within 10 per cent, and 85 per cent of the readings fell within 20 per cent, of the average for the group. In general, in the present study, the greatest tendency to vary from the average was found in the systolic pressure in the thigh, followed, in order, by the diastolic pressure in the thigh in the horizontal position. The least variability was noted in the systolic pressure in the arm in the horizontal position and in the diastolic pressure in the arm in the standing posture.

That there is considerable variation in the difference between blood pressures in the thigh and arm can be seen from Table I. Thus, in the horizontal posture, the systolic differential pressure varied from −4 to +64 mm., with an average difference of 35 mm., and the diastolic differential varied from −20 to +60 mm., with an average difference of 27 mm. of mercury. In the upright posture, the systolic differential varied from −4 to +128 mm., and the diastolic varied from +2 to +104 mm.; the average for the former was 78, and, for the latter, 66 mm. of mercury. A negative differential pressure was observed in only two cases.

Table IV lists various values for the difference in blood pressure between the thigh and arm as observed by various authors. The average for all groups, including ours, is 31.6 mm. of mercury; that is, the blood pressure in the thigh averages that much higher than in the arm.

TABLE III

VARIATIONS OF OBSERVATIONS FROM THE AVERAGE FOR EACH POSITION

	PLACE	POSITION	AVERAGE PRESSURE		OBSERVATIONS ± 10 PER CENT OF AVERAGE		OBSERVATIONS ± 20 PER CENT OF AVERAGE	
			CASES	MM.	CASES	PER CENT	CASES	PER CENT
Systolic pressure	Arm	Lying	105	115	64	61.4	96	91.4
		Standing	96	115	55	57.3	87	90.6
	Thigh	Lying	107	150	56	52.3	86	80.4
		Standing	100	193	58	58.0	92	92.0
Diastolic pressure	Arm	Lying	105	77	62	59.4	86	81.9
		Standing	96	83	59	61.4	99	94.3
	Thigh	Lying	107	104	59	55.1	80	76.2
		Standing	100	149	71	71.0	85	85.0
Average			102	123	60.5	59.5	88.8	86.5

TABLE IV

COMPARATIVE STUDIES ON SYSTOLIC BLOOD PRESSURE DIFFERENTIAL BETWEEN THIGH AND ARM IN HORIZONTAL POSTURE

AUTHOR	YEAR	CASES	TYPES OF CASES	DIFFERENCE		METHOD
				AVERAGE	RANGE	
Burdick and others	1925	4	Normal	38	?	Photographic
Strang	1929	54	Normal	38	?	Auscultatory
Glasermann	1932	10	Normal	30	?	Auscultatory
		7	Anemia	53	?	Auscultatory
		26	Aortic regurgitation	46	?	Auscultatory
Cady	1939	75	Essential hypertension	38	6 to 88	Auscultatory
		75	Nonhypertensive	22	11 to 30	Auscultatory
Gambill and Hines	1941*	112	Miscellaneous† (including 2 hypertensive)	35	−4 to +64	Auscultatory

*Present paper is a report of the results of this study, which was conducted in 1941.

†One hundred ten of these had essentially normal blood pressure.

<div align="center">TABLE V</div>

<div align="center">CASES ACCORDING TO HIGHEST HORIZONTAL THIGH PRESSURE
BASED ON SIXTY-NINE CASES</div>

PRESSURE	LEFT THIGH BLOOD PRESSURE HIGHEST		RIGHT THIGH BLOOD PRESSURE HIGHEST		EQUAL BLOOD PRESSURE IN THIGHS
	CASES	AVERAGE, MM.	CASES	AVERAGE, MM.	CASES
Systolic	28	5	31	8	10
Diastolic	27	7	29	9	13

If one considers only normal persons, fairly close agreement will be found among various authors.

Although the blood pressure, on the average, appeared to be slightly higher in the right than in the left thigh, this difference does not appear to be significant except in certain cases in which there are unilateral lesions of the central nervous system. Comparative values between blood pressure in the right and left thighs in 69 of the 112 cases are listed in Table V.

In considering various factors which might affect the thigh-arm differential blood pressure, it seemed desirable to compare the effects of so-called spastic and flaccid types of involvement of an extremity.

Pitfield,[28] in a study of normal subjects and subjects suffering from organic cerebral lesions, chiefly hemiplegia, noted that the blood pressure in the limb contralateral to the cerebral lesion responded with much greater changes to tapping over the brachial artery than did the blood pressure in the homolateral limb. This change was chiefly in the diastolic pressure, which either rose or fell. These differences were not observed among his control cases. It was suggested that certain brain lesions may thus render the blood pressure in the affected limb more labile and less subject to the influence of higher vasomotor control.

With the foregoing in mind, a tabulation was made of cases in which there were unilateral cerebral or spinal lesions. There were eight such cases in this series. A rough grouping into those in which there were spastic, and those in which there were flaccid, types of involvement of an extremity was made. The results are listed in Table VI.

It was expected that possibly those in which there was spastic involvement might have a higher, and those in which there was flaccid involvement a lower, blood pressure in the affected than in the normal limb. This seemed to be true for Cases 47, 68, 72, and 94. In the other four cases this difference was less striking. Cases 47 and 68 are especially worthy of comment, for these patients had a considerably higher blood pressure in the spastic thigh than in the normal thigh. In these two cases, the differences were probably significant, for differences of pressure between the two thighs for the entire series of 112 cases were not nearly so great as among the foregoing cases. In

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TABLE VI

COMPARISON OF DIFFERENCES OF BLOOD PRESSURE (IN MILLIMETERS OF MERCURY)
IN THE TWO THIGHS IN THE STANDING POSTURE. INDIVIDUAL DIFFERENCES
IN EIGHT CASES IN WHICH THERE WERE UNILATERAL NEUROLOGIC
LESIONS, AND AVERAGE DIFFERENCES FOR RIGHT AND LEFT
THIGHS IN SIXTY-NINE CASES*

</div>

CASE	DIAGNOSIS	AFFECTED SIDE DIFFERS BY:		TYPE DISTURBANCE	
		SYS-TOLIC	DIAS-TOLIC	SPASTIC	FLACCID
47	Right spastic hemiplegia, 15 months' duration	+ 2	+28	+	
68	Left parkinsonism	+54	+38	+	
101	Right spastic hemiplegia, 7 years' duration. Very little residual	− 1	− 6	+	
107	Bilateral parkinsonism (left > right)	−18	+24	+	
88	Right spastic hemiplegia (ancient)	− 4	0	+	
72	Protruded disk (atrophy, decreased reflexes)	−46	−38		+
86	Protruded disk (atrophy, weakness of limb)	−12	+14		+
94	Atrophic left leg (since a child). Left patellar and Achilles reflexes much decreased; left abdominal reflex absent	−20	−16		+

*Average difference between right and left thigh in sixty-nine miscellaneous cases, including the above, was systolic, 6; diastolic, 8.

Cases 88 and 101 the extremity had been paralytic for years, and the blood pressures in the affected limb were not much different from those on the normal side. Could it be that blood vessels in the affected limb had readjusted their tonicity gradually over a period of years to harmonize with the general level of blood pressure?

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COMMENT

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Although the factors of excitement and discomfort from the use of the tight cuff may have contributed in some degree to the wide variations which were noted in blood pressure and pulse rate among some subjects, other factors would seem to be of greater importance. Outstanding among them would seem to be the differences of constitutional make-up among different persons which help determine the response of blood pressure in the resting, unstimulated states, as well as the response to an emotional or painful stimulus. Realization of this fact suggests greater caution in attributing declines or increases of blood pressure to the effects of a given therapeutic procedure. The factor of variability is even more important among those who have essential hypertension and among vascular hyperreactors without hypertension.

It is not within the scope of this paper to discuss the various hypotheses which have been advanced to explain the difference of blood pressure in the thigh and arm. We agree with Strang[16] that two components are apparently responsible for such differences: a hydrostatic and a dynamic component. It is the latter which permits vascu-

lar readjustment over a wide range, and which is necessary to meet the varying needs of the living organism.

The reason why, in two subjects, the blood pressure was lower in the thigh than in the arm is not understood. The blood pressures in these cases were checked several times with the thought that some error had been made, but none could be found.

SUMMARY

Blood pressure, pulse pressure, the difference of blood pressure in thigh and arm, and the pulse rate in 112 subjects in the horizontal posture showed great variability from person to person.

The tendency of the diastolic blood pressure to increase while the systolic blood pressure remained essentially the same on changing from the horizontal to the standing position is in agreement with the results reported by others.

Fifty-nine and five-tenths per cent of all blood pressures fell within 10 per cent, and 86.5 per cent fell within 20 per cent, of the average for the group. These results are almost identical with those of Strang.[16]

Differential blood pressures between thigh and arm revealed a wide range of values; the average was 35 mm., systolic, and 27 mm., diastolic, for the horizontal posture. Assumption of the standing posture resulted in a differential pressure of 78 mm., systolic, and 66 mm., diastolic.

No apparent correlation was noted between differential pressures and factors such as age, sex, or occupation.

No significant differences were found between blood pressures in the left and right thighs of normal subjects.

Knowledge of the range of blood pressure in the normal, nonhyperreacting subject, as contrasted to that in the normal, hyperreacting, or hypertensive, hyperreacting subject, is particularly important for those who are trying to evaluate therapeutic attempts to lower or raise the blood pressure.

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BLOOD PRESSURE IN THE ARM AND THIGH OF MAN

II. Hydrostatic Influences

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THE purpose of this study was to attempt to evaluate the hydrostatic factor in the changes of blood pressure which are associated with assumption of the upright posture. This is the second of a series of papers reporting the results of a number of different studies on a group of subjects. For a general discussion of purposes, criticisms, and techniques, the reader is referred to the first of this series of papers.[1]

Hill, Flack, and Holtzman[2] found a definite correlation between the theoretical and observed increases of blood pressure that occur on assumption of the erect posture. The theoretical increase due to hydrostatic pressure was nearly the same as the actual increase. Strang[3] made similar calculations, and expressed the opinion that the increase of blood pressure with change to the upright posture is due almost entirely to hydrostatic pressure, although he felt that a vasopressor homeostatic component may also contribute to the increase.

In the present investigation the influence of hydrostatic pressure was studied by three approaches. First, in 50 of the 112 subjects, the cuff on one thigh was inflated, before the subject stood, to a point well above the systolic blood pressure in the thigh in the upright posture. After the subject had stood for one minute the blood pressure in the opposite thigh was taken, after which the blood pressure was recorded on the side with the inflated cuff: the reading was made as this cuff was deflated. Readings were repeated in the same order in each thigh one minute later for comparison. Although prior inflation of the cuff on one side does not obviate hydrostatic pressure, it does apparently modify, momentarily, the blood pressure immediately after the hydrostatic column is abruptly lengthened by deflation of the cuff.

Second, the approximate value of hydrostatic pressure at the level of the popliteal space was calculated in the upright posture by measuring the distance in centimeters from the left fourth intercostal space near the sternum to the lower border of the thigh cuff in the popliteal space. By means of the following formula, used by Strang, the value of hydrostatic pressure in millimeters of mercury was obtained:

$$\frac{\text{Distance in millimeters}}{13.6} \times 1.05 = \text{millimeters of mercury.}$$

In this instance, 1.05 represents the specific gravity of blood and 13.6 represents the ratio of the specific gravity of mercury to that of water. Thus, the calculated hydrostatic pressure was compared with the observed increase of pressure which occurred on standing. These calculations were done on 26 of the 112 subjects.

Third, the effect of elevation of the arm or thigh on the blood pressure was observed. In twenty-six cases the arm was elevated to an angle of 90 degrees with reference to the horizontal position, and the resulting blood pressure was noted at the end of one minute. In fourteen cases the thigh was elevated semipassively to angles of 35 and 90 degrees with the horizontal, and then the blood pressure was noted at the end of one minute. The latter procedure is open to criticism because one could not always obtain relaxation of the hamstring tendons. Variations of the contraction of these tendons could possibly affect the accuracy of the readings.

RESULTS

Use of the thigh cuff on one thigh in the first study showed a net decrease of 8 mm. (33 per cent) in the systolic, and a decrease of 17.6 mm. (10.8 per cent) in the diastolic, blood pressure; the opposite thigh was used as a control. The decrease of pressure was observed for only a few seconds during, and immediately after, deflation of the previously inflated cuff. Within thirty to sixty seconds after deflation of the cuff, the blood pressure on the experimental side was usually back to the level of the control thigh. The results are shown in Table I.

The foregoing observations are probably significant because it was found[1] that blood pressures while patients were in the horizontal posture were essentially the same in both thighs in most cases. The exact reason for the foregoing differences is not clear. One might reason that, while the cuff is kept inflated above systolic pressure in the upright posture, the vessels below the cuff are spared the internal stretching force which otherwise would be exerted by the hydrostatic pressure of the column of blood below the heart. They thus tend to relax. However, whenever the pressure in the cuff is lowered below the diastolic level, the full hydrostatic load of the column of blood above the cuff is thrown on the relaxed vessels below the cuff. They perhaps soon regain their constrictor tone under the influence of the resulting internal stretching force of hydrostatic pressure. In this connection one may recall that Bayliss,[4] many years ago, demonstrated that arteries contract and relax in response to variations of internal pressure.

The possibility that local vasodilating substances, such as histamine, might be elaborated in the leg rendered ischemic by the tight cuff and act locally on the vessels of that leg is to be considered.

TABLE I

DIFFERENCES IN ORTHOSTATIC BLOOD PRESSURE IN MILLIMETERS OF MERCURY
BETWEEN RIGHT AND LEFT THIGH, INDUCED BY INFLATION OF
ONE THIGH CUFF ABOVE SYSTOLIC PRESSURE PRIOR
TO ASSUMPTION OF ERECT POSTURE

CASES	PRESSURE	CONTROL DIFFERENCES	DIFFERENCES DUE TO CUFF	NET DIFFERENCES	DECREASE OF BLOOD PRESSURE DUE TO CUFF (%)
50	Systolic	−2.0	−10	− 8.0	3.0
50	Diastolic	−0.4	−18	−17.6	10.8

The results of the second study, carried out on twenty-six subjects, are to be found in Table II. Thus, the increase of blood pressure in the thigh on change of subjects from the horizontal to the upright posture, calculated on the basis of hydrostatic pressure, was 6.6 per cent higher for the systolic, and 2.5 per cent higher for the diastolic, pressure than the increases which were actually observed. Theoretically, one would rather have expected the observed pressure to be greater than the calculated pressure, if they differed at all. To explain the foregoing observation one might assume that an impairment of the compensatory homeostatic factors concerned in the regulation of the blood pressure occurs when the subject is moved to the upright posture. Strang, in his study of twenty-four subjects, found that the difference between the observed and calculated changes of blood pressure on assumption of the upright posture were less than 2 per cent. It would appear that most of the rise of blood pressure which occurs when subjects stand is the result of hydrostatic pressure. The potential role of homeostatic factors is, however, illustrated in some instances in which pressures in the upright posture exceed considerably the calculated or theoretical pressures.

The results of the third study, namely, the effect of semipassive elevation of arm and thigh, are revealed in Table III. Thus, the systolic pressure in the arm was lowered about 17 per cent, and the diastolic

TABLE II

BLOOD PRESSURE IN THIGH IN DIFFERENT POSTURE: OBSERVED COMPARED WITH THEORETICAL. AVERAGE VALUES IN TWENTY-SIX CASES

	POSITION	BLOOD PRES-SURE, THIGH	BLOOD PRES-SURE, STAND-ING MINUS LYING	HEART TO POP-LITEAL SPACE (CM.)	EQUIV-ALENT, MM. OF MER-CURY	THEO-RETICAL PRES-SURE	THEO-RETICAL PRES-SURE MINUS ACTUAL	DIF-FER-ENCE (%)
Systolic pressure	Lying Standing	152 197	45	75.6	58	210	+13	+6.6
Diastolic pressure	Lying Standing	106 160	54	75.6	58	164	+ 4	+2.5

TABLE III

EFFECT OF SEMIPASSIVE ELEVATION OF ARM OR THIGH ON BLOOD PRESSURE IN THAT ARM OR THIGH

	CASES	PRESSURE	HORI-ZONTAL	ELE-VATED 1 MIN.	CHANGE	CHANGE (%)	APPROXI-MATE ANGLE OF ELEVATION (DEGREES)
Arm	26	Systolic Diastolic	119 77	99 59	−20 −18	−16.8 −23.3	90
Thigh	14	Systolic Diastolic	160 111	148 96	−12 −15	− 7.5 −13.5	35 to 90 (Av. 66)

pressure was lowered about 23 per cent by such procedures. The systolic pressure in the thigh decreased, on the average, 7.5 per cent, and the diastolic pressure decreased 13.5 per cent on elevation of the limb.

That the decrease of blood pressure which occurs in the limb which is elevated may not be due entirely to hydrostatic pressure is suggested by the following observations made on one of us (E. E. G.): The control blood pressure when the thigh was in the horizontal position was 142/96. After elevation of the thigh to approximately 80 degrees for one minute, the pressure was 102/78. The foot was then flexed and extended in that position ten times during a period of ten to fifteen seconds. The pressure in the thigh immediately after this exercise was 100/58. The blood pressure one minute after assumption of the horizontal position was 138/88. Emptying of the venous reservoir or some other change as the result of the exercise must have affected the homeostatic component of blood pressure, for, obviously, hydrostatic pressure was constant before and after exercise.

SUMMARY

Placing a cuff around the thigh and inflating it above the level of systolic blood pressure before subjects assumed the standing posture resulted in a significant, but rather transient, lowering of blood pressure in that thigh when the blood pressure was measured during the period of deflation of the cuff. Possible explanations for this observation are suggested.

It appears that most of the increase which occurs in the blood pressure in the thigh when one stands is due to the influence of hydrostatic pressure. There is, however, in a few subjects a homeostatic component in such increases; this is variable, and is distinct from that due to hydrostatic pressure. This homeostatic component may be of considerable magnitude.

Elevation of the arm or thigh above the horizontal position resulted in a decrease of blood pressure in the limb; this is apparently also largely related to hydrostatic factors.

The posture of a limb in which the blood pressure is measured should be stated, particularly when the limb is not in the horizontal position. For obvious reasons, the horizontal position of the limb is the one in which blood pressure should be measured.

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BLOOD PRESSURE IN THE ARM AND THIGH OF MAN

III. Effect of Venous Engorgement

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WE HAVE been impressed with the observation that venous congestion often seems to result in an increase in the diastolic pressure. In some instances this may amount to several millimeters. The fact that some persons have this tendency, whereas others do not, requires clarification. The purpose of this study was to learn something about the effects of congestion, produced by various means, on blood pressure in the arm and leg while subjects were in the horizontal and erect (head-up) posture, and to study individual differences. Three types of study were performed, utilizing different groups of persons among the 112 people upon whom studies were reported in the first of this series of papers.[1]

STUDY 1

This study consisted of observing the effect of relatively prolonged engorgement of one leg, produced by keeping the pressure within the cuff about the thigh above the level of diastolic pressure, but 10 to 15 mm. below systolic blood pressure, for three minutes. The blood pressures during this time were measured in the noncongested and congested limb, in that order, at the end of the first and third minutes, and then again one minute after deflation of the congesting cuff. This study comprised twenty-four cases in which the limb was in the erect posture and fourteen cases in which the limb was in the horizontal posture.

Results.—Congestion of the leg which was in the erect, foot-down position produced a net decrease of 1 mm. of mercury (0.5 per cent) in the systolic pressure, as compared with that in the noncongested leg, which was used as a control (Table I). This is, of course, an insignificant change. The diastolic pressure, in contrast, increased a net average of 13 mm. (8.2 per cent), apparently as a result of the congestion. Congestion of the leg which was in the horizontal position produced a net increase of 3.4 mm. (2.2 per cent) in systolic pressure and 11 mm. (10.3 per cent) in diastolic pressure in that leg when compared with the changes in the noncongested leg. The values for the diastolic pressure are probably significant. In eight cases, congestion of one arm which was in the erect, hand-down position resulted in a net increase of 7.5 mm. in the diastolic pressure, with essentially no change in the systolic pressure.

TABLE I

DIFFERENCES IN BLOOD PRESSURE BETWEEN THE TWO THIGHS IN STANDING POSTURE
AFTER CUFF PRESSURE IN ONE THIGH HAD BEEN MAINTAINED FOR THREE
MINUTES BETWEEN SYSTOLIC AND DIASTOLIC LEVEL

POSITION	CASES	PRESSURE TYPE	CONTROL BLOOD PRESSURE	CON- GESTED THIGH	NONCON- GESTED THIGH	DIFFER- ENCE	NET CHANGE (%)
Standing	24	Systolic	204	− 4	−3.0	− 1.0	− 0.5
	24	Diastolic	158	+13	0.0	+13.0	+ 8.2
Lying	14	Systolic	156	+ 3	−0.4	+ 3.4	+ 2.2
	14	Diastolic	107	+18	+7.0	+11.0	+10.3

A study related to the foregoing, employing one of us (E. E. G.) as the subject, consisted of congesting one leg in the following manner: Two cuffs were placed around one thigh, the first high on the thigh and the second just above the knee. A control blood pressure reading, taken in the thigh while the subject was standing, was 200/160. The subject then lay horizontally, and the upper cuff was inflated to 90 mm. of mercury, after which he assumed the standing position. After one minute of congestion in this position the blood pressure in the congested thigh had increased to 224/192. The upper cuff was then completely deflated, after which a second measurement revealed a systolic blood pressure of 210 and a diastolic of 160. Thus, congestion was associated with an increase of 24 mm. in the systolic pressure and of 32 mm. in the diastolic pressure. Discomfort from the procedure was minimal.

STUDY 2

The second study utilized 41 of the 112 subjects referred to in the first of these papers.[1] Two and sometimes three successive measurements of diastolic pressure were made in the arm and thigh; the second and third were made within ten to fifteen seconds of the preceding one. After the first measurement of diastolic pressure had been made, the cuff about the limb, without further deflation, was reinflated a few millimeters above diastolic pressure; after this it was deflated slowly until the diastolic level was again found. These readings were made with the subject standing and with the arm dependent. By the foregoing maneuvers blood could enter the arm and thigh as a result of cardiac systole, but could not get out of the limb. Engorgement of the arm and leg was thus accomplished.

Results.—The second diastolic measurement averaged 3 mm. higher in the arm and 9 mm. higher in the thigh than the first (Table II).

TABLE II

COMPARISON OF TWO SUCCESSIVE DIASTOLIC PRESSURES, THE SECOND OBTAINED AFTER
QUICKLY RAISING CUFF PRESSURE BY 10 TO 15 MM. OF MERCURY IMMEDIATELY
AFTER FIRST DIASTOLIC READING. BASED ON FORTY-ONE CASES WITH
SUBJECT IN STANDING POSTURE

	FIRST READING (MM.)	SECOND READING (MM.)	DIFFERENCE (MM.)	CHANGE (%)
Arm	81	84	+3	+3.7
Thigh	155	164	+9	+5.8

STUDY 3

This study consisted in noting whether the diastolic pressure was significantly altered as a result of quiet standing for three minutes. Comparisons were made between the diastolic pressure in the thigh while it was horizontal, before and after the subject had stood for three minutes.

Results.—The mean results in thirty-three cases are revealed in Table III. Thus, standing for three minutes apparently did not have much effect on the mean blood pressure in the thigh in the entire group when readings were taken subsequently in the horizontal position. However, it must be realized that individual patients may show wide differences in the change in blood pressure which results from a change in posture. For example, there were differences of as much as a 30 mm. increase, or as much as a 34 mm. decrease, in the diastolic pressure in the horizontal posture after standing, compared to that before standing for three minutes.

TABLE III

COMPARISON OF DIFFERENCE IN BLOOD PRESSURE BETWEEN THIGH AND ARM IN HORIZONTAL POSTURE BEFORE AND AFTER STANDING FOR THREE MINUTES

		INCREASE (+) OR DECREASE (−) IN BLOOD PRESSURE DIFFERENCE, MM. OF MERCURY					
		AVERAGE DIFFERENCE AFTER STANDING		RANGE OF DIFFERENCE AFTER STANDING			
	CASE			1 MIN.		3 MIN.	
		1 MIN.	3 MIN.	MAX.	MIN.	MAX.	MIN.
Systolic	33	+4	−0.2	+12	−16	+32	−32
Diastolic	33	+2	−1.0	+30	−34	+30	−30

COMMENT

This study does not explain why some persons exhibit a considerable increase in diastolic pressure, whereas others show little or no change as a result of congestion. It does, however, indicate that such differences do exist, and that considerable differences may be found from person to person. The increase in diastolic pressure in response to congestion appears to be greater in the congested leg than in the congested arm.

We have gained the impression, which has not been proved, that those persons who have soft, flabby muscles, or who have been in bed for some time and who are in poor general condition, are prone to exhibit a greater increase in diastolic pressure and a greater tendency to a decrease in the intensity and clarity of the diastolic auscultatory sounds during congestion of the limb than do persons of the opposite type. It may be that venous tone and the venopressor mechanism[2] are more effective among those who have hard, muscular limbs, thus counteracting the tendency to venous engorgement.

Interestingly, the systolic pressure responds little or not at all to congestion. This suggests the possibility that the increase in diastolic pressure under such circumstances may be due to increased local arterial constriction in response to increases of venous pressure in the venous reservoirs. If the vessels of these reservoirs can increase their tone sufficiently, and if other factors constituting the venopressor mechanism can function effectively, venous return may not be much hampered. The venous reservoirs would be less engorged, so that the load distal to the arterial side of the vascular segment would be less. The arteries proximal to these reservoirs, which are subjected to less internal pressure, would tend to contract to a lesser degree. This might tend to lower the diastolic pressure. On the other hand, if the ability to increase venous tone in response to venous engorgement is defective, then the great venous reservoirs which are engorged as a result of the cuff which is obstructing venous return cannot empty themselves effectively. The increased venous pressure is transmitted backward toward the arterial portion of the circulation. To overcome this increased load and to restore the former arteriovenous gradient in pressure, there may be a rise of pressure in the arterial segments. Since systolic pressure does not increase much under these circumstances, the increase in diastolic pressure may be produced largely by local arterial constriction, rather than by an increase of cardiac output.

Defective arterial constriction in response to venous engorgement could be a factor in the failure of the diastolic pressure to increase in some persons during venous engorgement. However, one must also consider the possibility that such persons may have a highly effective venopressor mechanism, which would tend to counteract congesting influences. Such persons possibly can deal adequately with the extravascular burden at its very origin, with the result that little or no extra pressure is called forth in the arterial side of the circulation to maintain the proper arteriovenous gradient of pressure. These suggestions are offered merely as possibilities, evaluation of which would be quite difficult.

We believe this study indicates the desirability, when one is measuring blood pressure, of deflating the cuff as rapidly as possible, in order to obviate the error of relatively higher diastolic pressure which may result from slow or intermittent deflation of the cuff. If the level of diastolic pressure cannot be readily established at the initial deflation of the cuff, it would seem best to deflate the cuff completely, wait a few seconds, and then try again. Lewis[3] observed that, if the pressure in the cuff placed around a limb is raised in increments, the pressure in the veins distal to the cuff increases within a few seconds to the level of each new pressure induced within the cuff. The venous pressure could be increased in this manner to approximately the level of the arterial pressure. It may be that persons who fail to exhibit increases of diastolic pressure in the presence of venous engorgement within the limb are able to compensate adequately for such engorgement.

SUMMARY

The production of congestion of an extremity by means of a tight cuff usually results in little change in systolic blood pressure, but, in some cases, it may result in considerable increase in diastolic pressure and a decrease in the intensity of the diastolic auscultatory sounds in that extremity. It is not known why some persons exhibit these tendencies, whereas others do not. Possible mechanisms are discussed.

Slow or intermittent deflation of a blood pressure cuff below the level of systolic pressure may tend to increase the value of the diastolic blood pressure in some cases. Suggestions are offered to obviate this tendency.

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BLOOD PRESSURE IN THE ARM AND THIGH OF MAN

IV. BLOOD PRESSURE IN EXERCISED EXTREMITIES

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AFTER we had observed the effect of congestion on the blood pressure in the arm and leg,[1] it seemed desirable to learn what effect exercise, by supposedly reducing venous engorgement, would have on the blood pressure. To observe the effects of exercise, subjects, while standing, were requested to rise up and down on the toes ten times during a period of ten to fifteen seconds. At the end of·the eighth excursion the pressure within the pressure cuff around the thigh just above the knee was quickly inflated to a point above the level of systolic blood pressure; then, at the end of the tenth excursion, the subject remained as still as possible while the cuff was rapidly deflated. The blood pressure was measured by the cuff as it was being deflated. A second blood pressure measurement was made in this thigh one minute after the first, and, in some instances, a third reading was made three minutes after the first. These values were compared with the control blood pressures in the standing posture. Thirty-six of the 112 cases reported elsewhere[1] were studied in this manner.

TABLE I

THE EFFECT OF EXERCISE ON THE BLOOD PRESSURE IN THE THIGH, STANDING
POSTURE (RAISING UP AND DOWN ON TOES FOR TEN TIMES IN 10
TO 15 SECONDS). BASED ON THIRTY-SIX SUBJECTS

	CONTROL (MM.)	AT END OF EXERCISE (MM.)	1 MINUTE AFTER EXERCISE (MM.)	CHANGE DUE TO EXERCISE (MM.)	CHANGE (%)	RECOVERY IN 1 MINUTE (%)
Systolic	195	192	196	− 3	− 1.5	133.0
Diastolic	156	133	150	−23	−14.7	73.9

The major effect of such exercise was a considerable reduction in the diastolic blood pressure; the average reduction was 23 mm. of mercury (Table I). Whereas one minute after exercise there was an overshooting of the systolic blood pressure above the level prior to exercise, there was, during this time, recovery of only 74 per cent of the loss of diastolic pressure that had been produced by exercise. These points are illustrated in Fig. 1.

At first it was felt that the reason for the decrease in diastolic blood pressure after exercise might be an emptying of the venous reservoirs

due to the exercise. If this were entirely true, exercising the leg while the cuff was inflated to a point well above the level of venous pressure would be expected to obviate much of this fall in pressure. To test this idea, twenty-six subjects were exercised with and without the cuff inflated to a point between systolic and diastolic blood pressure (Table II). There was essentially no difference in the two experiments in the change which occurred in the systolic pressure, and not much difference in the change which occurred in diastolic pressure, although the decrease in diastolic blood pressure was definitely less when venous return in the thigh was prevented by use of the tight cuff during exercise. Theoretically, the venous reservoirs of the exercised legs could not be emptied because of the obstructing cuff. Obviously, other factors were concerned in the reduction of the diastolic pressure which followed exercise. This reduction, it should be emphasized, was quite evanescent, for, in most cases, the diastolic blood pressure was back nearly to normal within a minute or so after the subject ceased exercise.
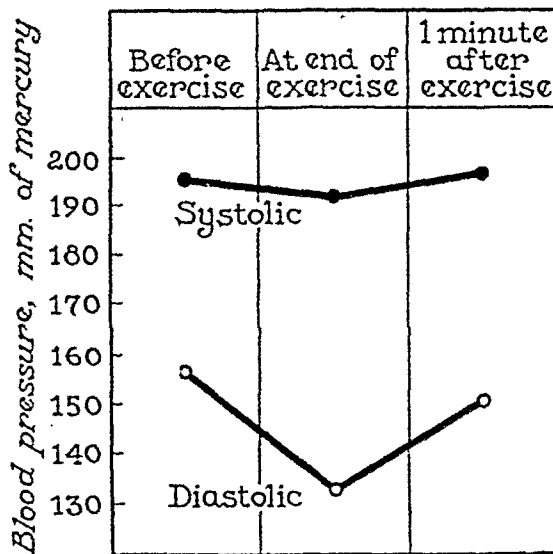
Fig. 1.—The effect of exercise of the legs (raising up and down on toes ten times in ten to fifteen seconds) on blood pressure in the leg while standing. Based on thirty-six subjects.

It is quite possible that such exercise reduces vascular tonus in the vessels of the extremity, perhaps by liberation of vasodilator substances or by reflex influences, or both. According to Anrep,[2] many substances associated with metabolism may produce vasodilatation. These influences include excess of carbon dioxide, histamine, and deficiency of oxygen. By the use of the hot-wire anemometer, Anrep showed that, during active exercise, there were a decrease of arterial inflow and an increase of venous outflow in the muscles which were being exercised. During relaxation these changes were reversed. In our studies the lowered diastolic pressure which was noted early in the relaxation which followed exercise may be related to relatively greater emptiness of the venous reservoirs produced by the muscular movements of exercise.

TABLE II

COMPARATIVE EFFECTS ON BLOOD PRESSURE IN THIGH IN STANDING POSTURE OF
EXERCISE WITHOUT AND WITH THIGH CUFF HELD BETWEEN SYSTOLIC
AND DIASTOLIC PRESSURES. BASED ON TWENTY-SIX CASES.
(EXERCISE CONSISTED OF RAISING UP AND DOWN ON
TOES TEN TIMES IN 10 TO 15 SECONDS)

| | THIGH BLOOD PRESSURE | | | CHANGE (MM.) | | CHANGE (%) | |
	CONTROL (MM.)	WITHOUT CUFF (MM.)	WITH CUFF (MM.)	WITHOUT CUFF	WITH CUFF	WITHOUT CUFF	WITH CUFF
Systolic	194	191	190	− 3	− 4	− 1.5	− 2.1
Diastolic	155	134	139	−23	−16	−13.5	−10.3

During this investigation it was observed that, while a blood pressure reading was being obtained in the thigh while the subject was standing immediately at the end of exercise, or during deflation of a cuff which had been kept inflated for one to three minutes above systolic blood pressure in the thigh, there was a loud, soft, fairly continuous, blowing, systolic bruit which first became audible at the level of the diastolic blood pressure and lasted 15 to 20 mm. below that level. This bruit, although continuous, was accentuated during passage of the systolic impulse along the artery. This bruit generally was absent when the cuff was reinflated thirty to sixty seconds after the initial deflation. It was often noted that an indefinite and faint diastolic pressure sound in the thigh could be made more definite and louder by exercising the leg for a few seconds.

One can best explain the aforementioned bruit by reasoning that blood coming from a region of constricted vessels which have good tone passes by the cuff abruptly into a region whose vessels presumably are comparatively relaxed and dilated, and more capacious as the result of exercise. The transient effect of any vasodilator substances or of reflex vasodilator mechanisms in producing decreases of vasomotor tonus is quickly replaced by vasoconstriction as the abrupt inflow of blood into the leg during relaxation of the muscles and deflation of the cuff results in an increase of the internal vascular stretching force. In this connection one is reminded of the observations of Bayliss[2] that arteries tend to relax when pressure within them is decreased and to constrict when this pressure is increased.

SUMMARY

Exercise of the legs resulted in a transient, but considerable, reduction in the diastolic blood pressure in the leg, but little reduction in the systolic blood pressure. The average reduction in the diastolic pressure was 23 millimeters. The systolic blood pressure was reduced, on the average, only 3 millimeters.

The prevention of venous return by means of a tight cuff about the thigh while it was being exercised had only a slight effect in preventing the decrease of diastolic pressure in the leg.

Other factors besides emptying of the venous reservoirs must be responsible for the decrease of diastolic pressure in the thighs which is noted soon after they are exercised. Certain vasodilator substances produced in the exercised extremity may play a role in such reductions of blood pressure.

A soft, continuous, blowing murmur, accentuated during passage of the systolic wave along the arteries, was often heard as blood pressure was being measured within the first few seconds after cessation of exercise, or while a cuff which had been kept inflated above the level of systolic blood pressure for a few minutes was being deflated.

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THE EFFECT OF RENAL VEIN OCCLUSION ON THE BLOOD PRESSURE OF THE DOG

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SINCE the evolution of the Goldblatt method[1] of producing hypertension by partial renal artery constriction, other experimental methods of interference with the renal blood flow have been used to affect the blood pressure. Page[2] has shown that envelopment of the kidney in a cellophane membrane leads to hypertension by virtue of perinephritis. Another method used for the production of hypertension is that of ureteral obstruction.[3] In this condition, as a result of resistance to urine flow, the pressure within the nephrons rises, the rise is transmitted through the kidney by virtue of the relative rigidity of the kidney capsule, and interference with renal blood flow ensues. However, the latter experiments have resulted in either transitory hypertension, with early death in uremia, or a mild, longer lasting blood pressure rise.[3] Still another experimental procedure has employed constriction of the renal vein. Such constriction, by obstructing outflow, interferes with the normal rate of blood flow through the kidney. Bell and Pedersen[4] succeeded in producing hypertension of about two months' duration in the rabbit by partial occlusion of the renal vein and placing a membrane around the kidney to prevent development of the rich venous collateral circulation which is known to follow renal vein occlusion. Dicker[5] and Braun-Menéndez[6] were successful in producing a slight pressure rise in the dog by partial venous occlusion alone, but this was transitory. A case of hypertension in a 12-year-old boy which was apparently due to occlusion of one renal vein by a thrombus has been reported by Perry and Taylor.[7]

The present study was undertaken in the endeavor to produce longer lasting hypertension by renal vein occlusion. For this purpose, in the long-term experiments, an attempt was made to apply enough constriction to prevent, if possible, early compensation by collaterals, and yet not to occlude enough to lead to progressive and fatal renal excretory insufficiency.

Since this type of interference with renal blood flow differs basically from the other types described above, pathologic studies of the kidneys were made to ascertain the effect of a long-standing increase of pressure within the organ upon the structure of the renal vessels.

METHODS

Blood pressures were measured with the Hamilton needle manometer.[8] The dogs were trained preoperatively, as previously described,[9] until control diastolic blood pressures showed variations of not more than ± 5 mm. Hg. Blood nonprotein nitrogen determinations were carried out by the method of Koch.[10] The operations were performed under sterile conditions on dogs anesthetized with nembutal or ether. In most cases the ligature method of Drury[11] was employed in partially constricting the veins. In some, a silver band, 2 mm. wide, was used for constriction. The venous occlusion was carried out bilaterally, or, more often, unilaterally, combined with contralateral nephrectomy either preceding or immediately following the venous occlusion. In the reoperations, carried out under similar anesthesia, visible collateral veins were ligated.

RESULTS

1. *Complete Occlusion of Both Renal Veins.*—Preliminary observations were made on bilateral, complete, venous occlusion in sixteen animals. All of these animals succumbed in from one to five days, with evidence of uremia. None showed hypertension. The kidneys at necropsy were intensely engorged; often, the renal capsule was ruptured, and in these cases there was extensive extrarenal hemorrhage.

2. *Partial Constriction of the Renal Vein.*—Bilateral, partial, venous occlusion was done in two experiments, and unilateral partial renal vein occlusion, with contralateral nephrectomy, in sixteen experiments. In eight animals, no blood pressure elevation was observed, although in five of these the nonprotein nitrogen rose temporarily to a varying extent. In the remaining eight animals a slight to moderate, immediate blood pressure rise resulted, reaching hypertensive levels in all. Three of the positive experiments are shown in Figs. 1, 2, and 3. The blood pressure rose immediately (within twenty-four hours) in all but one case, in which the rise began after a three-day lag. The pressure rise lasted from two to eight days. In only two instances was it accompanied by a rise in nonprotein nitrogen; in the other six the nonprotein nitrogen remained at its normal level.

In six instances the blood pressure returned to normal. In the other two instances, the pressure continued elevated to a moderate extent, but showed fluctuation. In Y 118 (Fig. 1), this later elevation persisted for 734 days and through two pregnancies. In Y 135 (Fig. 2), the blood pressure elevation lasted 60 days, until reoperation. In one of the dogs in which the renal vein was bilaterally occluded (X-5), one of the kidneys was removed 60 days later, and this was followed by elevation of the blood pressure for 39 days, when the experiment was interrupted by constricting the renal artery of this kidney for another experiment. As expected, a more marked hypertension occurred after the arterial constriction.

3. *The Effect of Reoperation to Reduce the Collateral Venous Supply of the Kidney.*—It soon became apparent from post-mortem examination
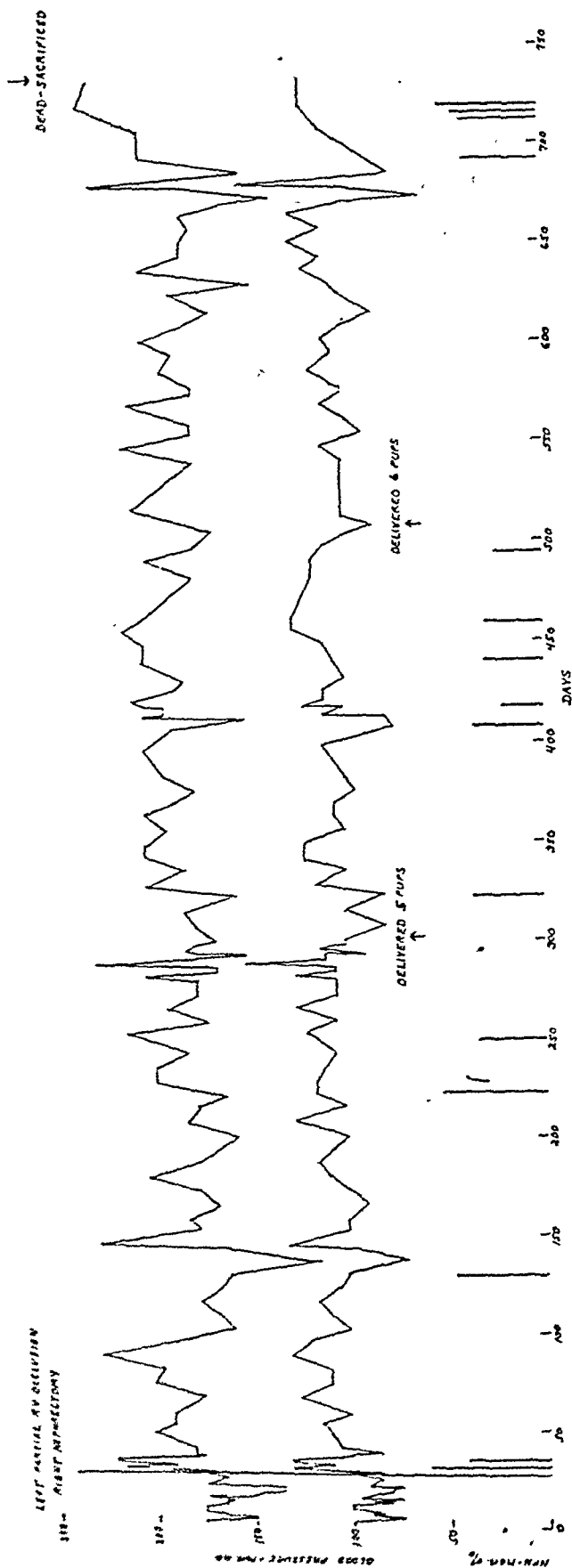
Fig. 1.—Blood pressure and nonprotein nitrogen in a dog (Y 118) which developed long standing, fluctuating hypertension after partial unilateral renal vein occlusion and contralateral nephrectomy. Top line represents systolic blood pressure, lower line diastolic blood pressure, columns at bottom, blood nonprotein nitrogen level. This animal went through two pregnancies during the course of the experiment. Time of parturition is indicated by arrows. RV = renal vein.
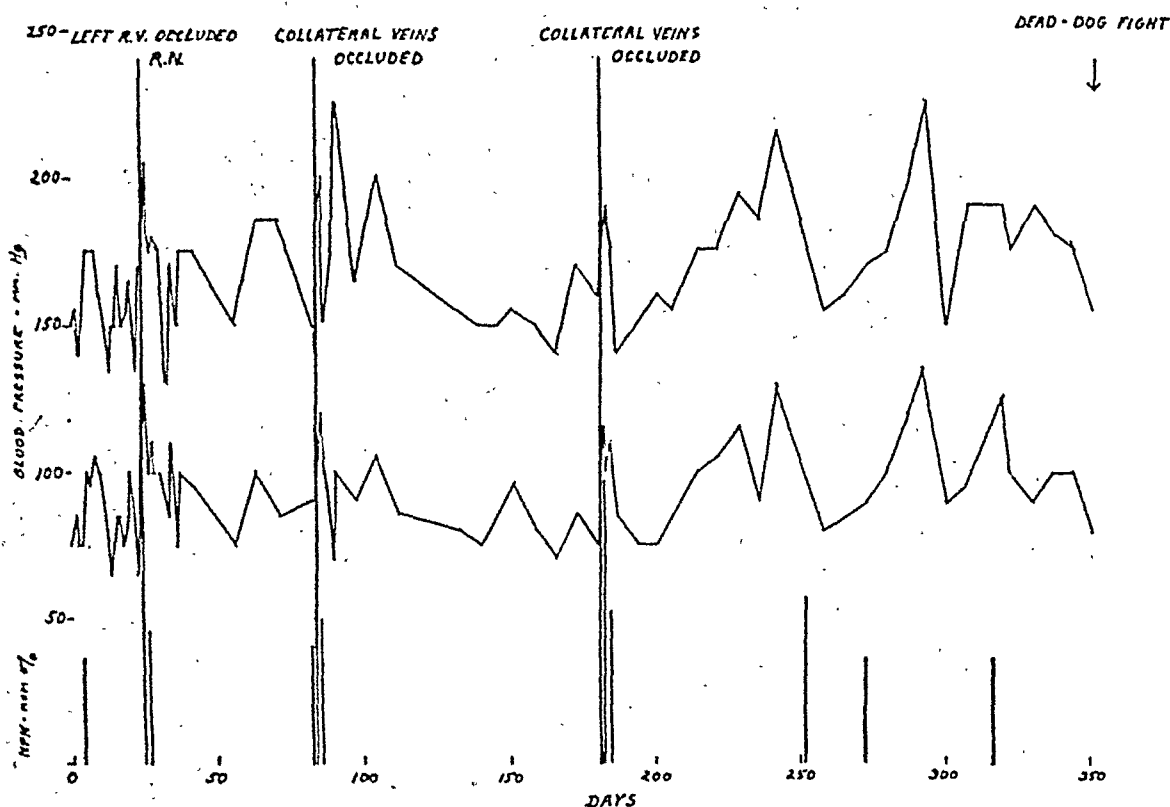
Fig. 2.—Blood pressure and nonprotein nitrogen in a dog (Y 135), showing the effect of unilateral renal vein constriction and contralateral nephrectomy and the effect of occluding the collateral capsular veins on two occasions by reoperation. R.V. = renal vein; R.N. = right nephrectomy.
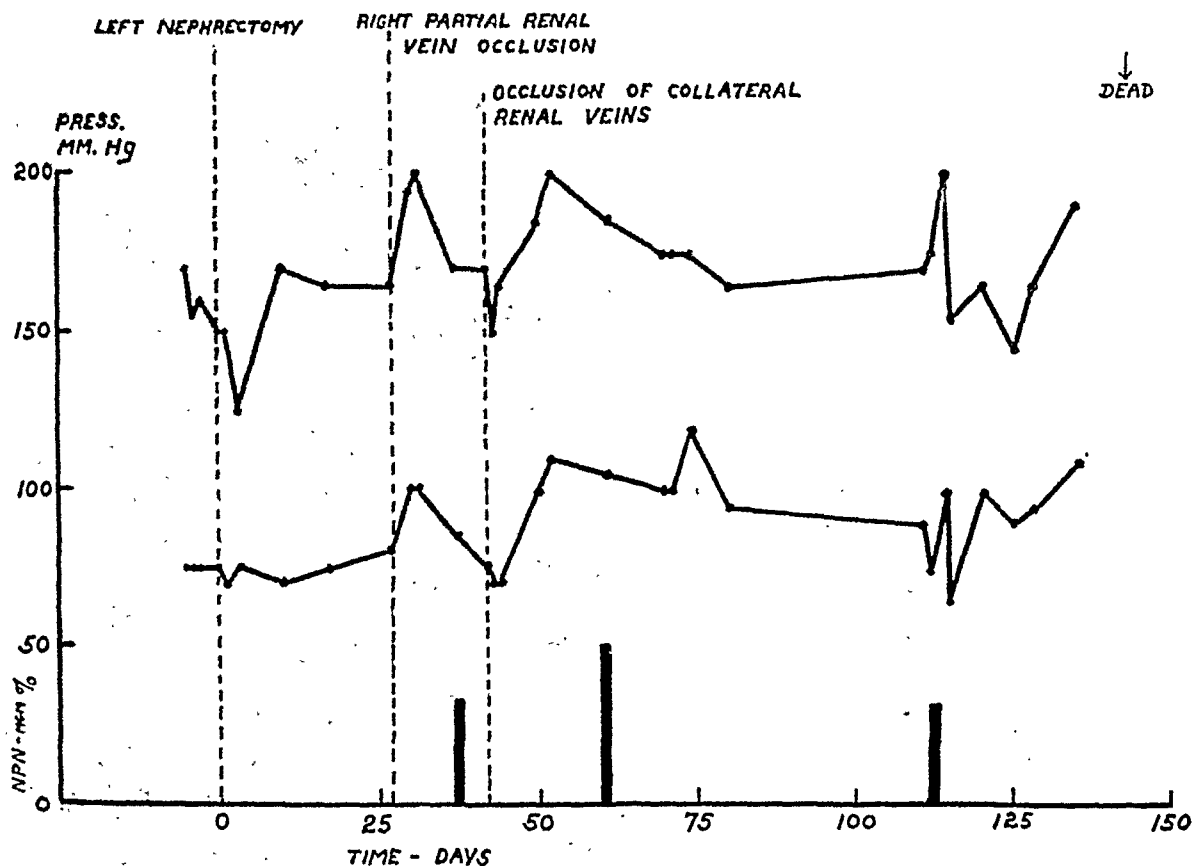
Fig. 3.—Blood pressure and nonprotein nitrogen in a dog (Y 32) after renal vein constriction of the remaining kidney and occlusion of the capsular collateral veins on reoperation.

of these kidneys that a very rich collateral venous network developed in the hilum and around the entire capsule. We reoperated on a number of these animals in an attempt to obliterate these collateral veins. Such reoperations were done once on four animals, without sustained hypertension after the initial venous occlusion, and twice on three animals, one with, and two without, sustained hypertension after the initial venous occlusion.

The first reoperation was done anywhere from 15 to 76 days after the initial operation. In four, neither transitory nor prolonged blood pressure elevation occurred. In the other three, an immediate blood pressure rise developed, lasting from two (Fig. 2) to ten days; in the latter this appeared after a seven-day lag (Fig. 3), but in the others the rise was immediate. In two of these animals, this immediate rise was succeeded by a later, fluctuating, moderate hypertension lasting 70 and 101 days, respectively.

Five animals were subjected to a second reoperation to obliterate the venous collaterals; this was done 75 to 278 days after the first reoperation, and three of these animals showed a transitory, immediate hypertension lasting one to three days (Fig. 2). In two, this was succeeded by a long lasting, fluctuating hypertension of moderate degree (176 [Fig. 2] and 400 days' duration, respectively).

Gross and microscopic examination of the kidneys was carried out.*

Grossly, there was a large amount of scar tissue around the site of ligation. Large collateral veins were abundantly distributed to the capsule and renal pelvis. The kidneys were bound down frequently by operative adhesions, which, in two instances of long standing hypertension (Y 32 and Y 118), actually distorted the shape of the kidney. In no instance was the renal artery found to be constricted or distorted by the scar tissue, and its lumen was widely patent and free of thromboses in every case. The kidneys were found to be somewhat paler than normal, but the blood vessels were more clearly evident than usual.

Microscopically there was evidence of chronic passive congestion, with the blood vessels widely dilated and engorged. The connective tissue was slightly increased and the tubular epithelium showed various degrees of cloudy swelling. No significant changes in the glomeruli were noted. Slight thickening of Bowman's capsule was observed occasionally. Small focal hemorrhages, with foci of lymphocytic infiltration, were also present. No significant changes in the renal arteries, arterioles, or veins were noted in any case, even in those animals which exhibited the longest and most marked hypertension.

DISCUSSION

It is clear from these results that, when the obstruction to renal venous flow is too great, as with complete occlusion of both renal veins, progres-

sive renal excretory insufficiency develops and the animal dies of uremia. Apparently the flow from the kidney is so impaired in this condition that the amount of the humoral mediator of hypertension which enters the blood stream is insufficient to cause any change in blood pressure. Such renal impairment, with no elevation in blood pressure, again illustrates the discrete relationship between hypertension and renal excretory insufficiency.[12] When the obstruction is too slight, however, not enough interference occurs in renal blood flow to initiate the production of a sufficient amount of the humoral mediator of hypertension to cause a blood pressure change. Unilateral obstruction, intermediate in degree, when accompanied by contralateral nephrectomy, produces at least temporary hypertension. This is accompanied by a mild, transitory impairment of renal function. The disappearance of the hypertension and azotemia is apparently due to the development of a rich venous collateral circulation, opened up by the elevation of renal venous pressure. Such venous collateral formation may occur more rapidly than collateral renal arterial supply, and may help to explain the more transitory nature of this type of hypertension. The speed and degree of collateral vein formation vary considerably from dog to dog. The effect of the collateral circulation can be retarded by operative ligation, in one or two stages, of the venous channels which develop, thus increasing the possibilities of producing a longer lasting hypertension.

Thus, hypertension lasting 734, 101, 70, 39, and 400 days, respectively, was produced in five dogs. In a sixth dog (Fig. 2), hypertension for 60 days, followed by an interval of 98 days of normal blood pressure and another period of hypertension of 176 days, occurred. However, these repeated operative procedures increase the chances of the development of a secondary connective tissue proliferation around the kidney.[13] By its contraction, this process acts in a manner similar to the perinephritis which follows envelopment of the kidney by a membrane. In fact, it has been shown that the attempt to increase the blood supply to the kidney by myopexy is ineffective in preventing hypertension for the same reason, i.e., capsular scar tissue formation, with compression.[13] In view of the multiplicity of factors involved, variability in results of such experiments are therefore not unexpected.

It has been established that essential hypertension in man often is associated with renal arteriolosclerosis.[14] Occasionally, however, renal biopsies in cases with human essential hypertension fail to reveal these lesions.[15] However, these renal vascular lesions have not been found in long standing, experimental renal hypertension, whether produced by renal artery occlusion[16] or by perinephritis.[17] The absence of renal arteriosclerosis in the former has been explained by the fact that the constriction of the renal artery prevents the hypertension from appearing in the renal arterioles. If the perinephritis occludes the main renal artery at the hilum or smaller arteries of the cortex, the same explana-

tion would apply. The absence of arterial change might have a similar explanation in our experiments with renal vein occlusion, for perinephritis occurs. This, if it is the explanation, must have involved the smaller cortical vessels, for the main renal artery was found unobstructed at necropsy. Further, resistance of species may play a role, for Goldblatt[15] has been unable to find arteriosclerosis anywhere in the body of the dog, except the eyeball, after long standing hypertension resulting from renal artery constriction. Thus it might well be that the dog is not a suitable animal in which to induce arteriosclerosis by long standing blood pressure elevation. The results with chronic renal vein occlusion may be germane to the mechanism of the hypertension which sometimes develops during congestive heart failure. In congestive failure there is sometimes a protracted elevation of venous pressure which can affect the kidneys in much the same way as in these vein occlusion experiments. However, in congestive failure it is not possible to compensate for this by the development of collaterals because the venous pressure elevation is universal in the systemic circuit. These experiments, therefore, may serve to account for one mechanism by which hypertension appears in congestive failure.

CONCLUSIONS

1. Complete bilateral obstruction of the renal vein leads to death in uremia, with suppression of renal function. No rise in blood pressure is observed.

2. Partial renal occlusion sometimes leads to mild, transitory hypertension which is soon dissipated by the formation of an extensive capsular venous network. In one dog, however, this procedure led to moderate, fluctuating hypertension which lasted over two years.

3. Reoperation and reocclusion of the collateral veins which develop is occasionally effective in producing a more severe and long lasting hypertension (of several months' duration). This may be due to effective interference with the venous drainage of the kidney, or to compression of the kidney by the scar tissue around the hilum and capsule which follows reoperation.

4. No permanent vascular changes were found in the kidney which might be related to arteriosclerosis, even in those animals with the more severe and longer lasting hypertension.

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MOMENTARY ATRIAL ELECTRICAL AXES

I. Normal Sinus Rhythm

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THIS paper describes a method of study of the atrial electrical impulse which may be used on persons who have normal hearts, or on patients who have abnormalities in the size, shape, or position of the heart, or of the site of impulse generation. Results obtained under abnormal circumstances will be reported later.

In 1921, Lewis, Drury, and Iliescu[1] employed simultaneous chest leads in an effort to demonstrate, on patients, the presence of a circus movement in atrial flutter and fibrillation. Their clinical data appeared to substantiate the conclusions which they had derived from preceding animal work. Lewis placed his leads on the chest wall in such a fashion that the electrical axis of the atrium could be measured from moment to moment in the sagittal, horizontal, and frontal planes. The electrical axes and the manifest electrical potential at each moment were calculated by means of the Einthoven triangle, and, from the data obtained from each plane, a three-dimensional circus movement was postulated for flutter, and an irregular, variable circus pathway for atrial fibrillation.

Our facilities did not permit us to take three simultaneous leads as Lewis, et al., did. We have, however, duplicated as nearly as possible their procedure, and have taken two leads simultaneously in each of the three planes by means of the Sanborn Tri-Beam Stetho-Cardiette. Each pair of leads may be taken simultaneously, i.e., Leads I and II, II and III, and I and III, and, by careful projection and matching, the three leads may be traced as though they had been taken simultaneously.

METHOD OF STUDY

In the *sagittal* plane, curves were taken by placing the right arm electrode over the manubrium, the left arm electrode over the xiphoid, and the left leg electrode on the back just to the right of the seventh dorsal spine. In the *horizontal* plane, the right arm electrode was in the left fifth intercostal space, near the left nipple, the left arm electrode in a corresponding position on the right side of the chest, and the left leg electrode on the back in the position mentioned above. The *frontal* projections were obtained by switching the left leg electrode from the back to the position over the manubrium sterni. The limb leads do not give a true frontal plane projection, as has been

pointed out by Schellong.[2] The appropriate position of the Einthoven triangle that is formed when the electrodes are thus applied is shown for each plane in Fig. 1. With the Sanborn instrument simultaneous leads were recorded: Leads I and II, II and III, and I and III. We were careful to place the electrodes so that the triangle formed was as nearly equilateral as possible. The tracings obtained were placed in an opaque projector, and were thrown, enlarged ten times, upon a piece of graph paper. They were traced on this graph paper, and the enlarged tracing was utilized for the measurements necessary to ascertain the electrical axis and the manifest potential, using the method of Carter, Richter, and Greene.[3]
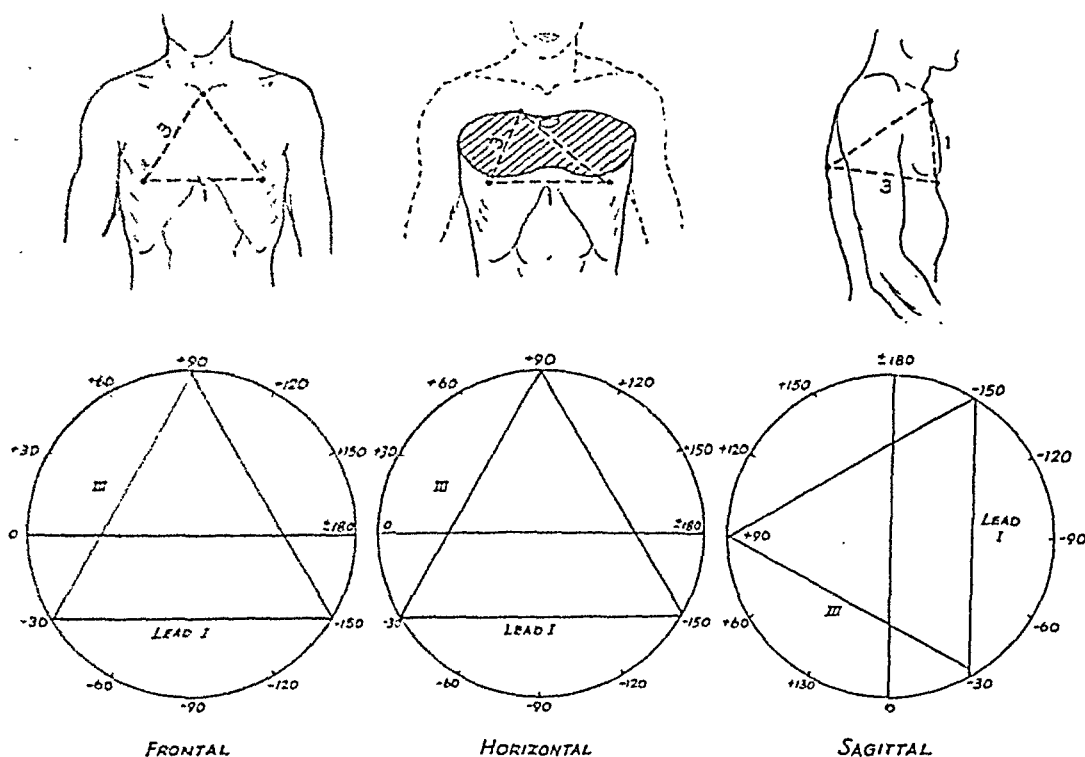
POSITION OF THE EINTHOVEN TRIANGLES IN THE 3 PLANES

Fig. 1.—A, Position of the electrodes, and the triangle formed in the three planes: frontal, horizontal, and sagittal. B, The position of the Einthoven triangles, and their angles, in the three planes.

The electrical axis calculated for each 0.01 second was plotted as shown in Fig. 2. It was assumed that the wave of depolarization travels a unit distance per 0.01 second, and the direction of the vector derived for each moment was plotted, beginning with the termination of the vector for the preceding time interval. The line thus obtained represents the consecutive momentary atrial electrical axes, and may be drawn for each of the three planes. By utilizing all three of the curves thus derived, one may visualize in three dimensions the momentary shift in the atrial electrical axis. The figures thus drawn or visualized have, of course, an anatomic basis, but are related only indirectly to the actual pathway of the electrical wave as it traverses the atrium.

Fig. 1 shows diagrammatically the details of the position of the electrodes on the chest wall. It illustrates the facts that (1) the triangles formed were usually not perfectly equilateral; (2) the plane designated as horizontal actually slanted down and forward; and (3) the posterior portion of the sagittal plane was slightly to the right of the midline. Fig. 2 shows the simultaneous records of Leads I and III in each plane, as derived from a normal young man. Below these tracings are graphed for each plane the consecutive electrical axes for each 0.01 second. In this case the atrial electrical activity lasted 0.11 second.

The curves for the frontal and horizontal planes show reasonable agreement, indicating that during the first 0.05 to 0.06 second the curve progressed forward and downward; later the axes inscribed a curve pointing to the left and downward. In the sagittal plane the vectors representing the electrical axes curved forward and down for 0.04 second, and after this ran nearly straight down. The photograph represents an effort to depict these movements in a single three-dimensional figure. The shadows show the projections of the "actual" axes upon the frontal and sagittal planes, thus approximately reproducing the curves actually obtained from the electrocardiograms taken in these planes. The position of the camera does not quite permit visualization of the curve in the slanting horizontal plane.

It must be emphasized that each segment of the curve represents only direction and time. The magnitude of the manifest potential cannot be shown without additional pictorial features, such as variation in the width of the line, and it was felt that this would unnecessarily complicate the figures. The use of a unit segment for each time interval in each plane cannot take into account the fact that the planar diagrams are projections of the "actual" electrical axis, and hence could not be equivalent on each plane. For this reason, there will be discrepancies when the "actual" axis is deduced from its three projections. In spite of all these deficiencies, the general trend of direction of the electrical axis is readily apparent in each instance.

Data obtained in this fashion depend, for their absolute value, upon the validity of the hypothesis originally advanced by Einthoven. Experimental proof of the validity of Einthoven's triangle is lacking. Fahr,[4] in 1920, mentioned briefly the fact that he had performed experiments on cadavers which showed that the Einthoven triangle was accurate to within ±10 degrees. There is abundant evidence[5] that the hypothesis cannot be justified absolutely for the human heart, because of the fact that the heart is not in the center of an equilateral triangle, and that the electrical properties of the tissues concerned do not fulfill the hypothesis. In spite of the theoretical and practical objections to the use of the Einthoven triangle, it has served profitably for valuable clinical experimentation.
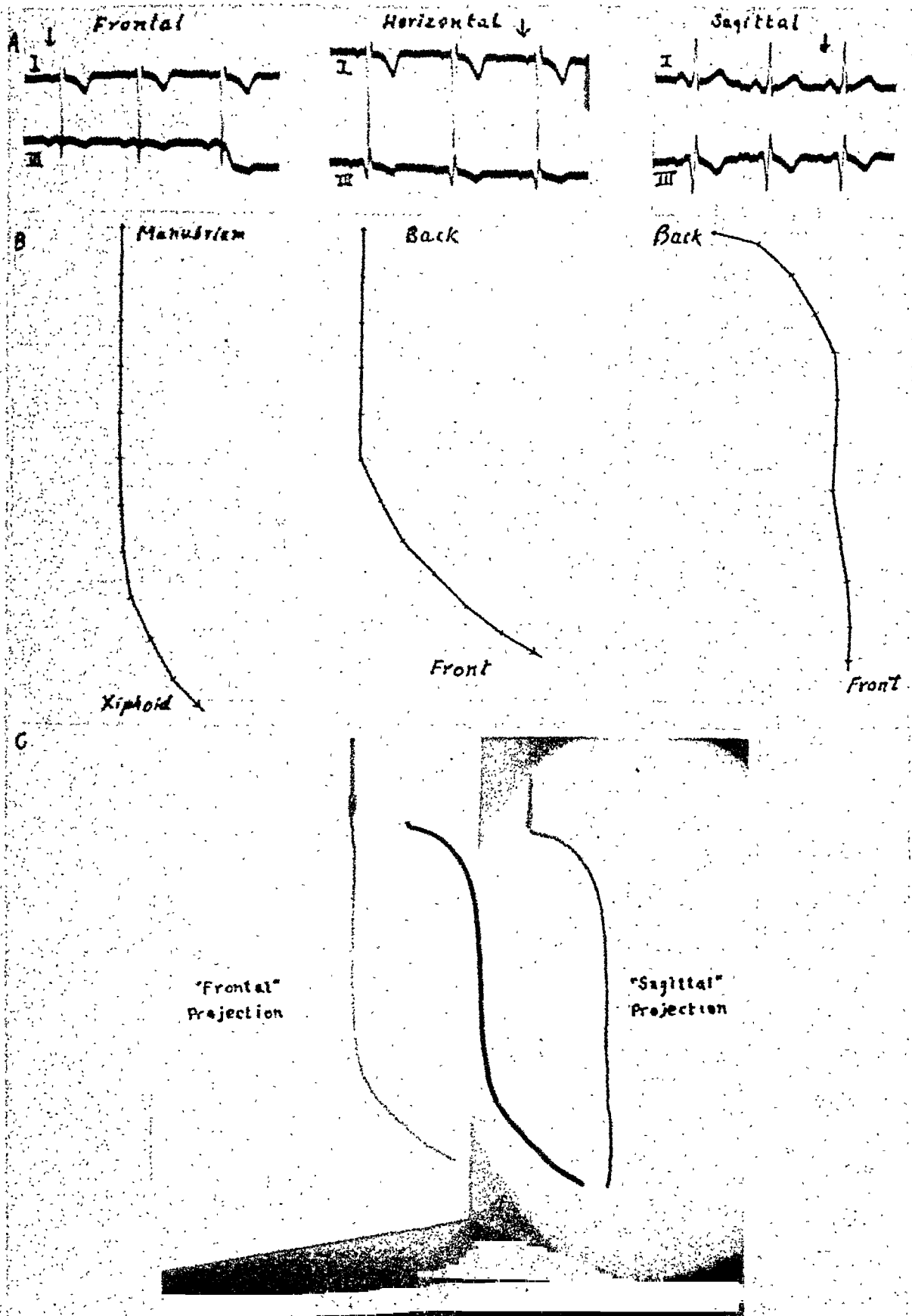
Fig. 2.—*A*, Simultaneously recorded Leads I and III for each plane, frontal on the left, horizontal in the middle, and sagittal on the right. *B*, Curves for each plane, representing the direction of the atrial axes for each consecutive 0.01 second; see text *C*, Photograph of a three-dimensional model in which the black wire represents the atrial axes. The shadows represent the projection on the frontal plane (left) and sagittal plane (right). They approximate the original curves for these two planes, shown above. The curve for the horizontal plane was utilized in arranging the position of the wire, but could not feasibly be reproduced by a third shadow.

Fig. 3 shows simultaneous tracings of the atrial complexes in Leads I and III, in each plane, taken on a normal male medical student. Lead II has been drawn in by carefully matching the projection of Leads II and III on the graph paper. For comparison, Lead II was calculated from the values for I and III, and is shown by the dotted line. The data employed are summarized in Table I. In the horizontal and frontal planes, the tracing drawn from the calculated data agrees quite well with Lead II as actually obtained. In the sagittal plane, however, there is considerable discrepancy. This has been found to be the case with other patients. Therefore, the curves derived from the sagittal plane are probably less accurate than are those in the other two planes. The ease with which the data from the three planes may usually be combined into a three-dimensional figure indicates to us that there is great practical usefulness in the Einthoven triangle hypothesis.

The theoretical aspects of vector analysis have been thoroughly discussed by Schellong[2] in his recent monograph. Weber[6] and Burger[7] made early studies of the momentary change of direction of the ventricular electrical axis. Mann[8] first attempted to derive a monocardio-

TABLE I

PLANE	TIME (SECONDS)	LEAD I	LEAD II OBSERVED	LEAD II CALCULATED	LEAD III	ANGLE (DEGREES)
Frontal	0.01	0.1	−0.3	−0.5	−0.6	− 82
	.02	0.2	−1.8	−1.8	−2.0	− 86
	.03	0.0	−2.8	−3.3	−3.3	− 90
	.04	−0.4	−4.8	−5.1	−4.7	− 94
	.05	−1.0	−7.6	−7.3	−6.3	− 98
	.06	−1.3	−8.2	−7.7	−6.4	−100
	.07	−2.0	−7.0	−8.0	−6.0	−105
	.08	−1.9	−4.7	−5.6	−3.7	−113
	.09	−1.8	−3.0	−4.0	−2.2	−117
	.10	−1.2	−1.5	−2.4	−1.2	−120
	.11	−0.5	−0.3	−1.0	−0.5	−120
Horizontal	0.01	0.2	−0.4	−0.4	−0.6	− 70
	.02	0.2	−1.4	−1.4	−1.6	− 83
	.03	0.3	−2.8	−2.6	−2.9	− 84
	.04	0.1	−3.8	−3.1	−3.2	− 88
	.05	−0.6	−4.1	−3.8	−3.2	− 98
	.06	−0.6	−4.0	−3.4	−2.8	− 99
	.07	−0.4	−3.4	−3.3	−2.9	− 97
	.08	−0.7	−2.7	−3.0	−2.3	−104
	.09	−0.2	−1.8	−1.5	−1.3	− 98
	.10	0.1	−0.9	−0.6	−0.7	− 97
	.11	0.1	0.0	−0.3	−0.4	−101
Sagittal	0.01	2.2	0.0	1.8	−0.4	20
	.02	3.8	0.6	2.5	−1.3	11
	.03	5.7	1.0	3.5	−2.2	5
	.04	8.3	0.8	4.6	−3.7	4
	.05	9.5	1.8	4.8	−4.7	0
	.06	9.4	4.0	3.9	−5.5	− 4
	.07	7.4	4.0	1.8	−5.6	− 13
	.08	5.4	3.5	0.4	−5.0	− 24
	.09	3.2	2.0	−0.4	−3.6	− 35
	.10	1.3	0.3	−1.0	−2.3	− 55
	.11	0.3	0.3	−0.4	−0.7	− 64

gram by calculation from the usual limb leads, and later devised an instrument whose beam was influenced by the potentials from all three leads.[9] Wilson and Johnston[10] employed the cathode-ray oscillograph for the same purpose. At about the same time, Schellong,[2] Hollmann and Hollmann,[11] and Guckes[12] began extensive clinical and experimental investigations of vector diagrams obtained from the human heart. These authors used differing leads and planes, but in each instance obtained tracings which represent the pathway, either in one plane or in three dimensions, of the ends of the momentary ventricular vectors of varying length, as the vectors rotate about a fixed point. Polar electrocardiograms were thus obtained instead of linear ones.
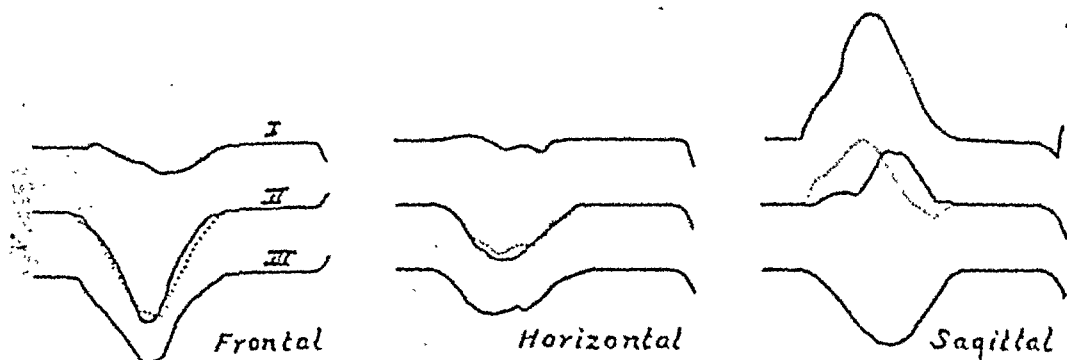
Fig. 3.—Reproduction of three leads in each plane, derived from a normal subject. Leads I and III were taken simultaneously, and traced upon graph paper. Leads II and III were superimposed by projection. The values of Lead II, as calculated from those of I and III, are shown by the dotted line. The data are in Table I.

By Mann's first method the vectors of the P wave may be satisfactorily measured. The methods which employ the oscillographic tube are valuable in studying the ventricular complexes, but yield such small complexes corresponding to the P wave that no conclusions may be derived from them. Our method of graphing differs, in that the electrical axis for each 0.01 second follows that for the preceding instant, rather than lying by its side. Our graph also differs from those employed by Lewis, although his data, when graphed by our method, give curves which are, in general, in agreement with ours.

EXPERIMENTAL RESULTS

Normal Persons.—The curve in Fig. 2 shows the momentary shifts in the atrial electrical axis in one normal person. Fig. 4 shows the models of six curves derived in a similar manner from normal male medical students. In the *frontal* plane most of the curves pass down and to the left in a rather uniform fashion. In one, however (Fig. 4, *f*), the curve moved to the right at an angle of −72° before turning down and towards the left; in this case fluoroscopic examination showed an unusually prominent right atrium, but no other indication of heart disease was detected. In the *horizontal* plane the curve forms an arc which moves forward and to the left, but with considerable variation. The early portion may point, as it did in one instance, slightly to the

right (−74°) before turning to the left; or the axes in the first few segments may point as much to the left as −140°. The terminal portion of the curve shows variation between −104° (forward and slightly to the left) and ÷160° (to the left and slightly backward). The curves obtained in the *sagittal* plane are consistent in that they usually move down, and, at first, forward; the terminal segments may turn, varying
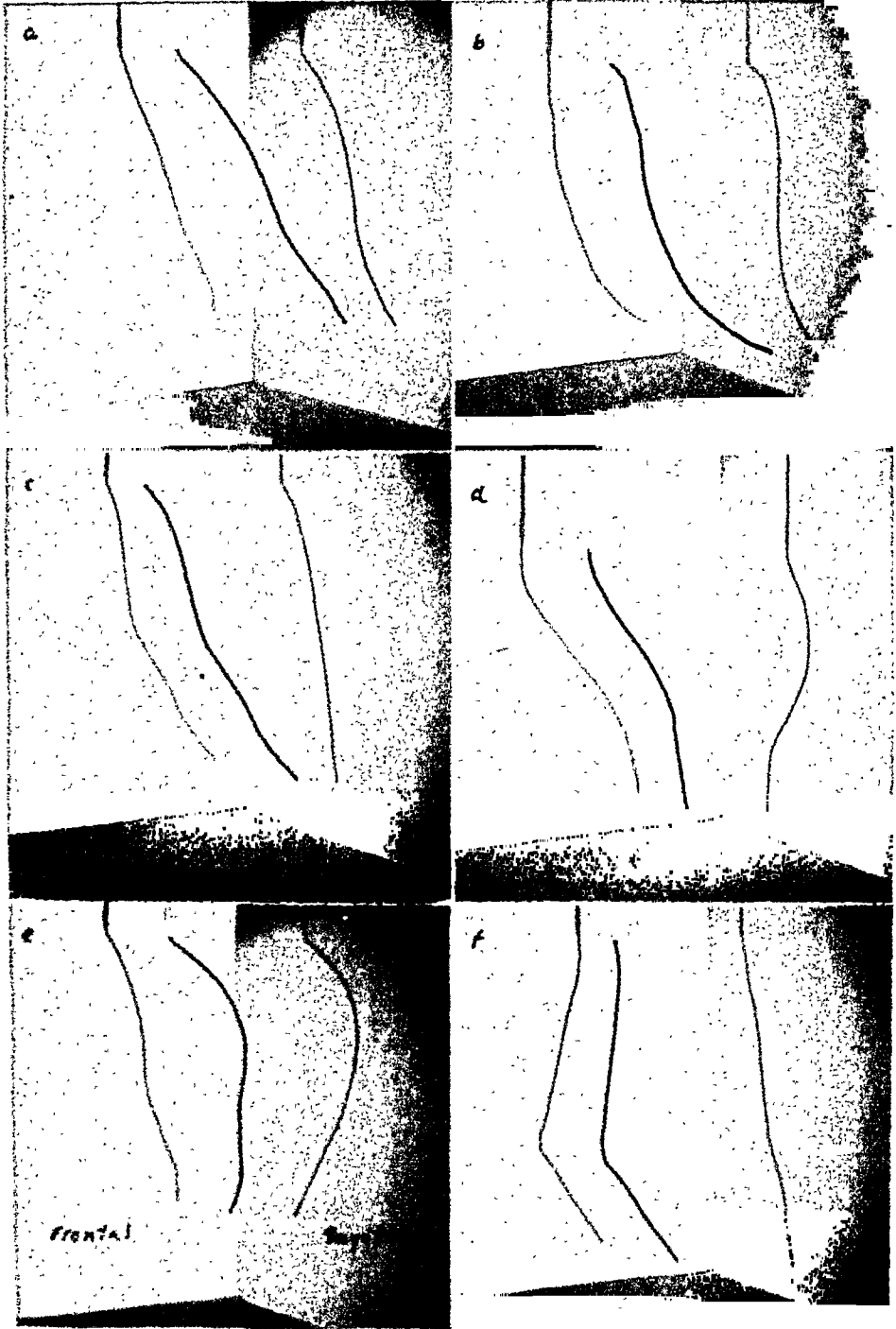
FIG. 4.—Atrial axes for consecutive 0.01 seconds, derived from normal young men, as described in the text and illustrated in Fig. 2.

from −90° (straight forward) to +30° (slightly backward). In one instance the curve in the sagittal plane showed a slight backward convexity. In general, normal persons appear to yield curves which are smooth and simple.
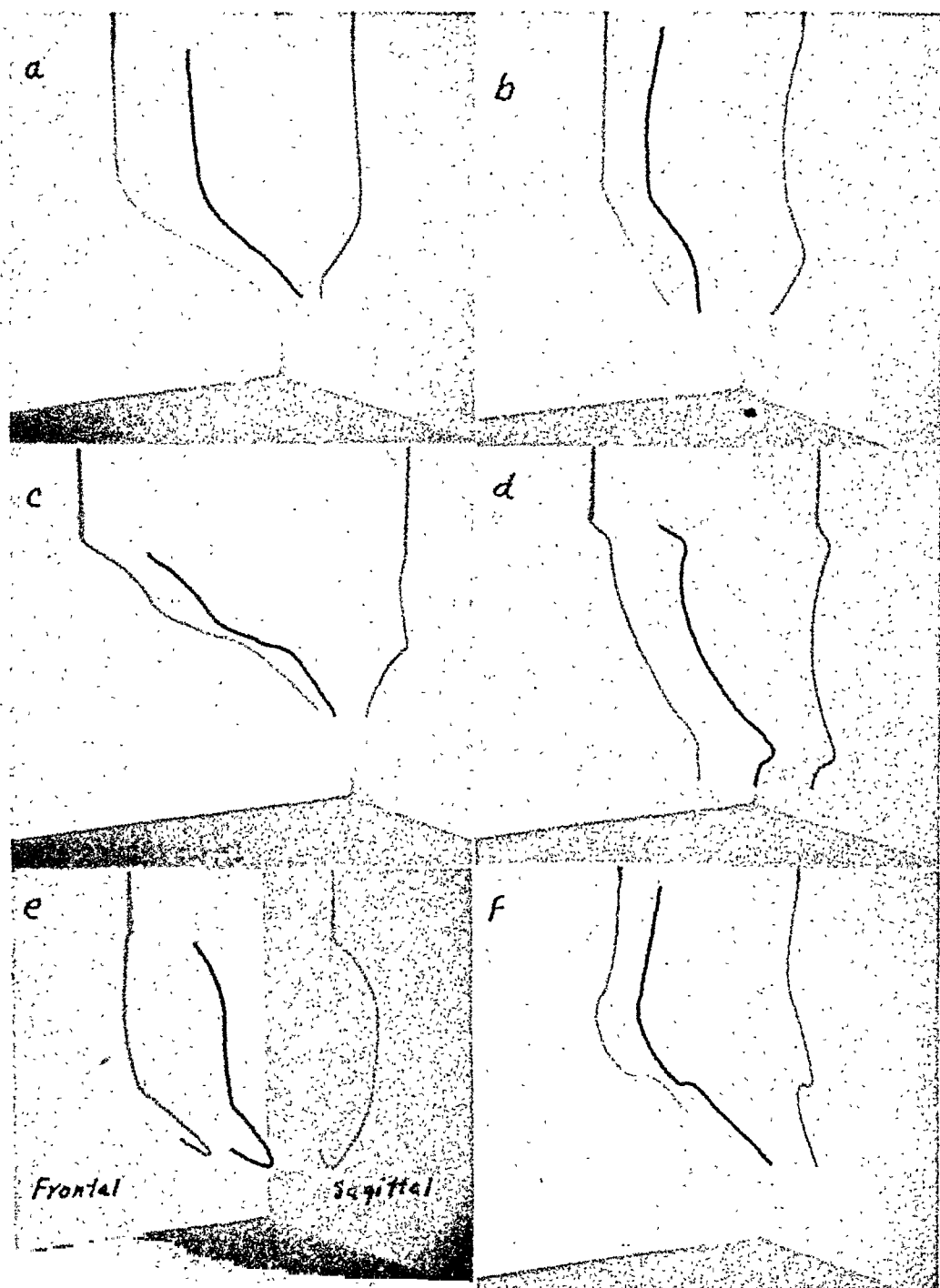
Fig. 5.—Consecutive atrial axes from patients with hypertensive and arteriosclerotic heart disease.

Patients With Heart Disease.—Fig. 5 shows six examples of the type of curve derived from patients with arteriosclerotic and hypertensive heart disease. The complexity of the curves fails to show, however, invariable correlation with the severity of the heart disease as judged by clinical standards. Thus, the curve in Fig. 5, *a,* is smooth, simple,

and devoid of complexity; it is the record of atrial activity in a case of hypertensive heart disease and congestive heart failure, with left bundle branch block and a QRS interval of 0.20 second. The curve in Fig. 5, *d*, is from a hypertensive patient with right bundle branch block of the Wilson type. The other tracings were derived from patients with clinical evidence of extensive myocardial disease. We regard the complexity of these curves, with their multiple changes in contour and
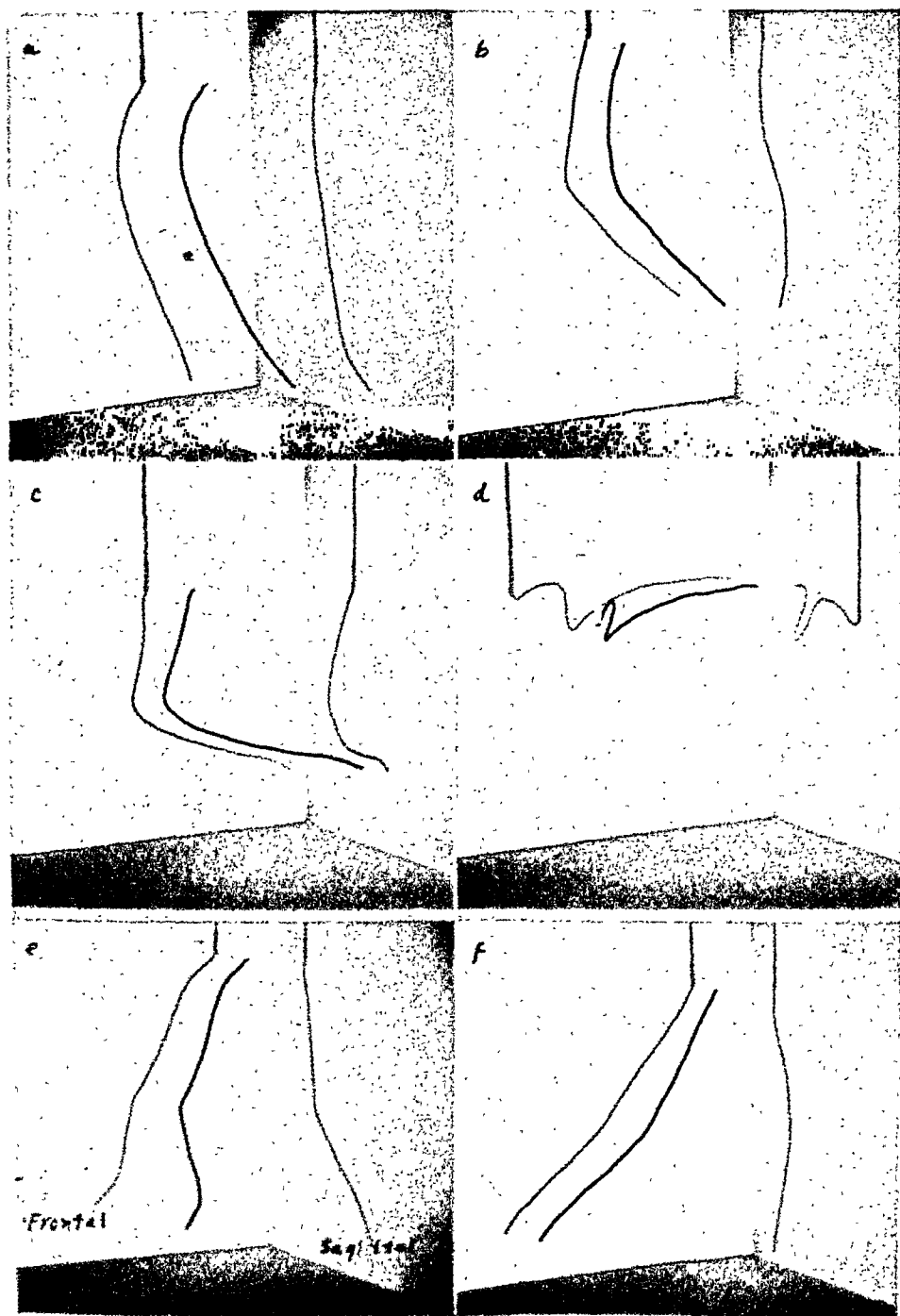
FIG. 6.—*a, b, c*, and *d*, Atrial axes in cases of mitral stenosis: see text. *e*, Dextroposition of the heart. *f*, Congenital dextrocardia.

direction, as a probable indication of disease of the atrial muscle, with conduction defects.

Two other types of anatomic abnormality are shown in Fig. 6. Fig. 6, *a, b, c,* and *d,* shows the curves from four patients with mitral stenosis. In Fig. 6, *a* and *b,* the curves move to the right and down, later turning to the left. Both patients had mitral stenosis of moderate grade. The curve in Fig. 6, *c,* is from a patient who had high-grade mitral stenosis, moderate aortic regurgitation, and congestive heart failure. Here the pattern of the two preceding curves is repeated in a more conspicuous manner. We suspect that this type of initial shift to the right of the atrial axes is to be connected with the dextroposition of the right atrium which occurs in such patients as a result of enlargement of the left atrium and the right ventricle. The patient from whom the curve in Fig. 6, *d,* was derived also had mitral stenosis and aortic regurgitation, but, in addition, had an acute exacerbation of rheumatic fever. We feel that disturbances in conduction through the atrial musculature, incident to acute rheumatic myocarditis, probably played a significant role in producing the bizarre curve obtained.

Dextroposition of an otherwise normal heart in a patient with extensive cystic disease of the left lung produced the changes illustrated in Fig. 6, *e,* in which the atrial axes move down, forward, and to the right. A similar but smoother curve was obtained (Fig. 6, *f*) from a young man with situs inversus and dextrocardia.

COMMENT

Presumably, the course of these curves is determined by the site of the pacemaker, and also by the physiologic and physical status of the atrial musculature. Anatomic circumstances make it reasonable to believe that the impulse originating in the sinoatrial node must spread down and to the left, and that the electrical axis, which is the resultant of the lines drawn perpendicular to the advancing wave of negativity or polarization, probably moves in a similar manner. Further study may make possible an exact correlation between the electrical axis and the electrically active portion of atrial muscle, similar to the analysis of the QRS complex made recently by Gardberg and Ashman.[13] However, it seems reasonable to anticipate that a change in the position of the pacemaker, a shift in the position of the heart, enlargement of one or both atria, and myocardial disease interfering with normal conduction will alter the curves of the electrical axes. Further study will be devoted to this, but, at this time, our interest is directed toward the general types of normal curves and their change of contour in certain disturbances of the atrial mechanism.

SUMMARY

Curves derived from patients with normal hearts show, in general, a shift of the consecutive atrial electrical axes down, forward, and to the left. The variations in this typical pathway are illustrated in Fig.

4, as well as one exception to this rule, in which there was a shift toward the right before the curve turned to the left.

Patients with myocardial disease may show a similar, smooth curve, or, more often, will yield curves which are complex, with multiple changes in direction and contour. Acute myocardial disease, as well as chronic myocarditis, may cause conduction defects which markedly alter the curve.

Patients with enlargement of other chambers of the heart which has pushed the right atrium toward the right, or, presumably, with enlargement of the right atrium itself, show curves which point to the right before turning to the left.

Dextroposition caused by disease in the lung or pleural space, or congenital dextrocardia, will produce curves which point entirely down and to the right.

Correlation of curves obtained by this method from persons with normal and diseased hearts with roentgenologic and necroscopic data is being undertaken. They are described at this time primarily for the purpose of setting up a standard for comparison with curves obtained from patients with atrial flutter, atrial fibrillation, and paroxysmal tachycardia, which are discussed in the second paper of this series.

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Clinical Reports

CHRONIC CONSTRICTIVE PERICARDITIS DUE TO A FOREIGN BODY (NEEDLE) IN THE PERICARDIUM

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CASES of constrictive pericarditis of traumatic origin are rare. Glenn[1] recently reported a case as a result of a crushing injury to the chest in an automobile accident. Warburg,[2] in an extensive review of the literature, cites three cases of traumatic origin, one of which was of dubious authenticity. Cases have been reported of bullets in the pericardium,[3] and migrating fish bones lodging in the pericardium, producing acute fibrinopurulent pericarditis.[4, 5] However, a review of the literature has failed to reveal any case of chronic constrictive pericarditis due to a foreign body. It is, therefore, believed that the following case of constrictive pericarditis caused by the lodgment of a surgical needle in the pericardium will be of interest.

REPORT OF CASE

T. B., a 46-year-old fireman, was admitted to the Veterans Hospital, Bronx, New York, June 23, 1942, with a diagnosis of "cirrhosis of the liver with possible obstruction." His chief complaint was that he had been losing weight since Christmas of 1941, but, despite that fact, his abdomen continued to be large and occasioned the ridicule of his fellow workers. He feared that he had an abdominal tumor, although he stated that he did not believe his abdomen had increased in size. In the preceding six months he had lost 30 pounds in weight. He complained of an excessive amount of gas, which was accompanied by belching. He had always been stout; his usual weight was 220 pounds. He had an uncomfortable sensation in his abdomen. When he walked rapidly, his "belly shook." In 1935, while fighting a fire, he fell three stories and sustained a fracture of the right knee, the left forearm, and several ribs on the left side. He was taken to a hospital, and, while undergoing an anesthetic preliminary to correction of the fractures, the patient stated that his heart stopped. He was given an injection in the third right intercostal space in the parasternal line. The needle broke off. An incision was made to recover the needle, but the attempt was unsuccessful. While in the hospital undergoing treatment for his fractures, he was told that pericardial effusion had developed. A physician wished to operate on his heart, but he was dissuaded against any operation by another physician. A roentgenogram in the patient's possession, taken in December, 1935, revealed evidence of pericardial effusion. The patient stated that, since the accident, his blood pressure had been low, usually about 88, systolic. He did not complain of shortness of breath or pain in the chest on admission. Seven years before

he did have pain in the right side of his chest, but this disappeared completely. In December, 1941, he had an attack of phlebitis in the right leg, and still had occasional swelling of this extremity. He drank about three to four glasses of beer weekly. He never drank wine or hard liquor. This was confirmed by the patient's wife.

Examination disclosed a somewhat undernourished, well-developed, white male, with a protuberant abdomen, who did not appear to be acutely ill. His temperature was 98° F., his respirations, 20, and his weight, 188½ pounds. There was no dyspnea or cyanosis in the erect or sitting position. In the supine position, the patient's face and neck assumed a dusky, cyanotic hue. He did not become dyspneic. Examination of the fundi disclosed slight retinal arteriosclerosis. The veins of the neck were moderately distended in the erect position; in the supine position they were markedly so. The thorax was of medium size and configuration, and the lungs were normal. There was a 3 cm., linear, postoperative cicatrix in the third right intercostal space in the parasternal line. Heart: The point of maximum intensity of the apex impulse could not be palpated. The heart was not enlarged to percussion, the sounds were muffled, and the second sound was reduplicated at the apex. There were no thrills or murmurs. The blood pressure was 112/76-76. The pulse rate was 92. No appreciable peripheral arteriosclerosis was present. There was no paradoxical pulse, Broadbent's sign, or systolic retraction at the apex. The abdomen was swollen moderately. A fluid wave was present, and the liver was 1½ inches below the costal margin on the right. It was not tender. The spleen was not enlarged. There were no other masses. Extremities: The left arm was 2 inches shorter than the right. There was incomplete ankylosis at the elbow joint, and extension was limited to 165 degrees. Supination was moderately curtailed. There was a 4 by 3 cm. cicatrix over the right knee. Flexion of the right leg at the knee joint was limited to 90 degrees.

Laboratory studies: A roentgenogram of the chest (Fig. 1) on June 30, 1942, showed that the heart and lungs were within normal limits. There was evidence of a pleuropericardial adhesion at the base. Two linear densities were seen at the border of the pericardium at the right. These had the appearance of broken fragments of a needle. The roentgenologist said that they appeared to be embedded within the pericardium or myocardium. Fluoroscopic examination revealed marked diminution of the phasic excursions of the heart. The pulsations were feeble. There was no change in the heart size or position with deep inspiration or expiration. Esophageal study with barium showed no definite abnormalities. There was no evidence of esophageal varices. The electrocardiogram (Fig. 2) revealed a diphasic T_2; T_3 was inverted. QRS_3 was of low voltage, and S_2 was prominent. The venous pressure measurement, using the direct method, on July 3, 1942, was 33.5 cm. (normal, 4 to 12 cm.). On July 9 the venous pressure was 27.5 cm. The arm-to-tongue time on July 3, 1942, using sodium dehydrocholate, was 18 seconds (normal, 12 to 18 seconds). On July 9 the arm-to-tongue time was 10 seconds. The arm-to-lung time (ether) on July 3, 1942, was 6 seconds (normal, 4 to 6 seconds). Bromsulfalein test: 5 minutes, 85 per cent; 30 minutes, 5 per cent. The icteric index was 12.5. The van den Bergh was 0.1 mg. The serum albumin was 5.2, the serum globulin, 2.8. There was a mild anemia. Chemically, the blood was normal. The urine was negative. The blood Wassermann and Kahn reactions were negative.

Diagnoses of "chronic constrictive pericarditis of traumatic origin, with enlargement of the liver and ascites, Class III, and foreign body, metallic, right side of the chest" were made. The cause of the constrictive pericarditis was believed to be either the needle in the pericardium or the original trauma, i.e., the fall. Pericardiectomy was recommended. However, the patient wished some time to arrange his affairs, and he was discharged July 14, 1942.
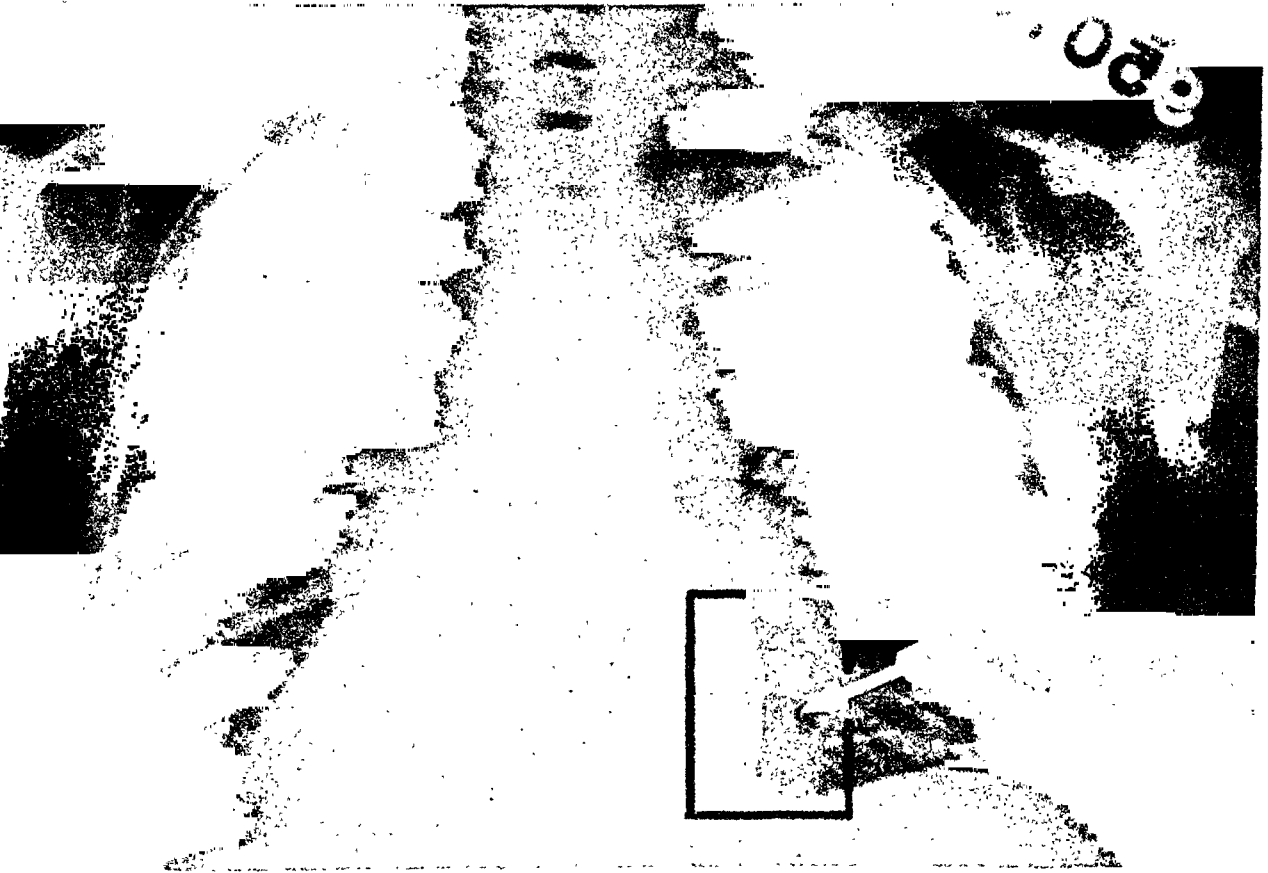
Fig. 1.—Arrow indicates needle in pericardium.
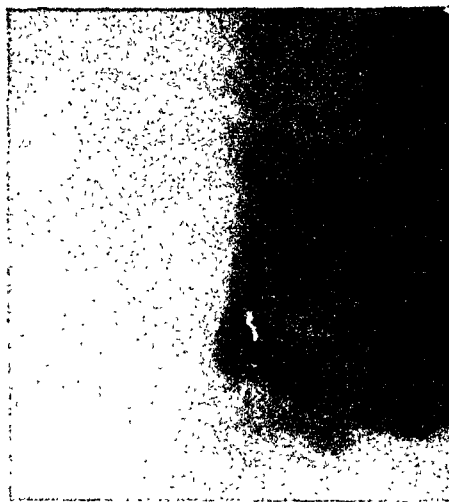
Fig. 14.—Enlargement of section showing needle fragments.

On July 22, 1942, the patient entered the Mt. Sinai Hospital, New York City, Surgical Service of Dr. Harold Neuhof.* On July 23, 1942, abdominal paracentesis was done and 8,000 c.c. of straw-colored fluid were removed. The blood pressure was 105/80.

Operation by Dr. Harold Neuhof: Under nitrous oxide, oxygen, and ether, oro-endotracheal anesthesia, an incision was made in the right third intercostal space, in a transpleural approach. Evidence of an old inflammatory process was noted in the intercostal muscles. The right side of the heart was exposed, and the amplitude of the cardiac excursions was seen to be distinctly diminished. A large pericardio-diaphragmatic adhesion was seen and divided. The pericardium was thick, indurated, and densely adherent. The epicardium and pericar-
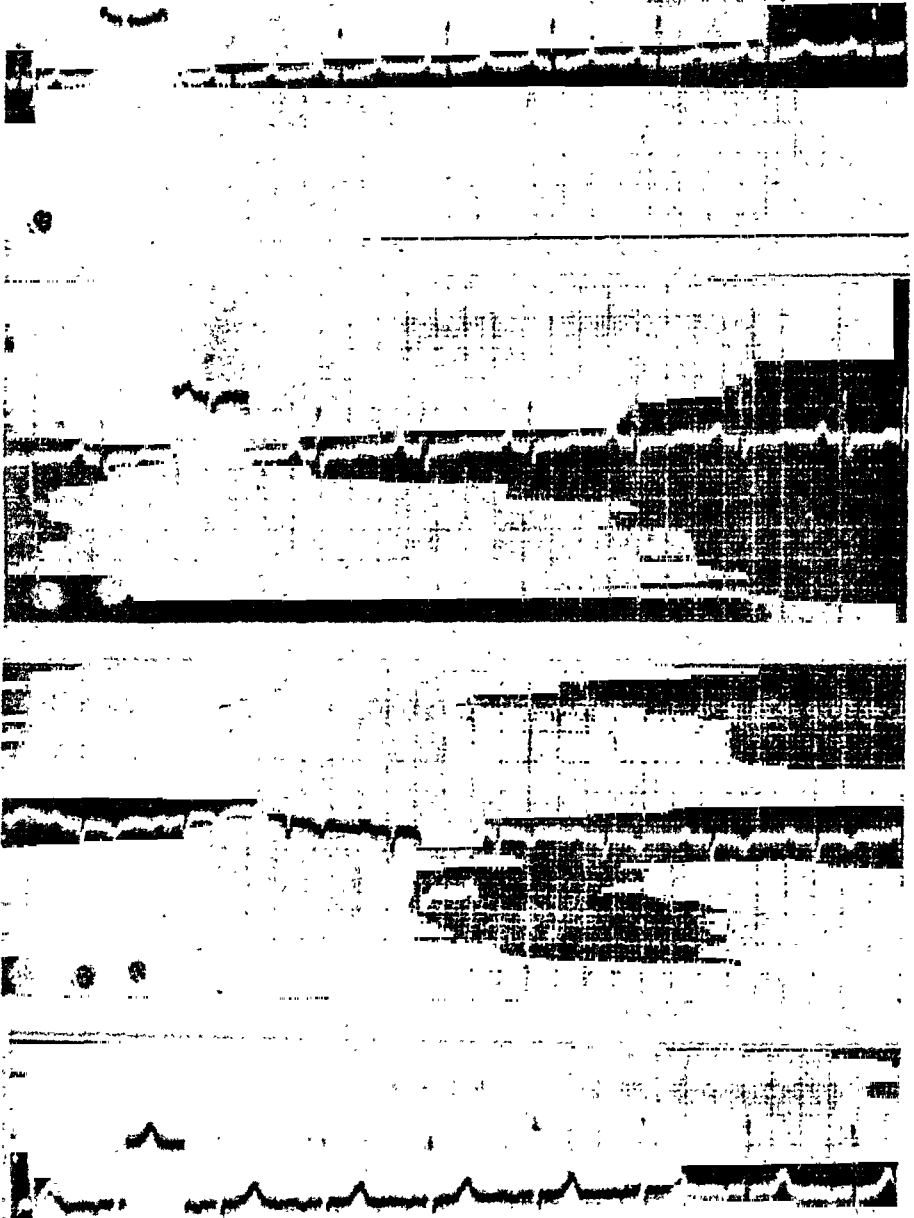
Fig. 2.

dium were completely fused over the exposed portion of the heart. The pericardium over the right side of the heart was dissected away and removed. In the region of the inferior vena cava. the needle was found in two pieces in a dense, fibrous sheath, and removed. No attempt was made to free the left side of the heart. Sulfathiazole was placed in the operative field. Closed drainage was instituted in the right axilla and the chest wound was closed.

The patient left the operating room in excellent condition. His blood pressure at onset of the operation was 104/64. When the pericardium was opened, the blood pressure rose from 84/45 to 128/80. This rise in blood pressure was maintained throughout the postoperative period, indicating that the heart had been effectively freed. The day after the operation the patient developed a purulent bronchitis which rapidly progressed to bronchopneumonia. Despite the administration of oxygen, several bronchoscopic procedures, sulfadiazine, and supportive measures, the patient died on the third postoperative day, July 26, 1942. Death apparently was caused by suppurative bronchopneumonia.

The pathologist reported fragments of thickened pericardium, showing marked fibrosis, with hyalinization and focal lymphocytic infiltration. The second fragment of pericardium showed the foreign body (needle).

An autopsy was not obtained.

SUMMARY AND CONCLUSIONS

A case is presented in which chronic constrictive pericarditis developed six years after the accidental deposition of a portion of a surgical needle in the pericardium.

White[6] observes that trauma resulting in hemopericardium may leave chronic adhesive pericarditis. This is due to fibrosis following organization of the blood. In this case the pathogenesis is probably related to two factors:

1. The development of an acute inflammatory process, beginning at the site of the needle. This is substantiated by evidence of an old infection of the intercostal muscles along the course of the needle, and by the development of a pericardial effusion about two weeks after the injury.

2. Fibrosis due to chronic irritation of the pericardium because of the needle itself. This idea is supported by the fact that the thickening, fibrosis, and induration of the pericardium were maximal at the locus of the needle.

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REPORT OF A CASE OF PAROXYSMAL VENTRICULAR TACHYCARDIA, WITH NO DEMONSTRABLE ORGANIC HEART DISEASE, WHICH PRODUCED ATTACKS OF SYNCOPE

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PAROXYSMAL ventricular tachycardia is a condition that is not often encountered. Although it has been reported for many years, writers usually point out the fact that it is a rare condition. It is not common in association with organic heart disease; much less commonly is it found in cases in which no organic cardiac lesion is evident. In a recent review[1] of thirty-six cases from the records of the Heart Station of the Boston City Hospital, the incidence was one in every 1,800 electrocardiograms. Of the thirty-six cases, there was only one in which ventricular tachycardia occurred without heart disease (1 in 64,800 tracings).

By far the greatest number of cases in which ventricular tachycardia occurs are cases of arteriosclerotic heart disease, often associated with hypertension. It occurs after coronary thrombosis and in rheumatic heart disease. It would therefore be expected that the largest incidence would be found among older patients. However, it may occur at any age. Amberg and Willius[2] reported its occurrence in a female infant of 15 months who had cardiac hypertrophy of unknown origin. Wolferth and McMillan[3] reported four cases of paroxysmal ventricular tachycardia, and the ages of two of the patients were 18 and 20 years, respectively. In both cases there was evidence of organic cardiac disease.

CASE REPORT

C. J. H., a soldier, 27 years of age, was admitted to the Camp Myles Standish Station Hospital Jan. 9, 1943, complaining of attacks of dizziness, palpitation, and occasional syncope. Physical examination disclosed a medium-sized man who was worried over these distressing attacks which had been coming on since October, 1942. Heart examination disclosed occasional premature systoles. There was no enlargement, the heart sounds were of good quality, and no murmurs were heard. The blood pressure was 112/70.

Past History.—Diphtheria at the age of 5 years; scarlet fever at the age of 6 years; chicken pox at the age of 8 years. There was no history of rheumatic fever. He had never had attacks prior to October, 1942. In civil life he had been a cigar salesman.

Family History.—His father had had pulmonary tuberculosis, but is now considered cured. His mother and eight brothers are living and well.

The patient said that his first attack occurred early in October, 1942. He felt sudden dizziness, fullness of the neck, and a sense of weakness.

He continued to have attacks of this nature, and occasionally he lost consciousness. He always recovered rather promptly without ill effects, and was able to resume his duties where he had left off. The most severe attack occurred Nov. 7, 1942, while he was working at a mimeograph machine. He lost consciousness for several minutes (3 to 5 minutes, according to witnesses). When he recovered, he was able to continue to operate the machine and to finish the task to which he had been assigned. This attack prompted him to report to the dispensary, where he was observed, and later sent to a hospital. No diagnosis was made. After his discharge, he continued to have attacks and was admitted to the Station Hospital.

An electrocardiogram taken Jan. 23, 1943, showed rather frequent premature ventricular systoles, occasionally in couples (Fig. 1). The patient was observed for many days, but during his stay in the hospital he did not have any attacks. No diagnosis was made, except cardiac arrythmia due to premature ventricular systoles.
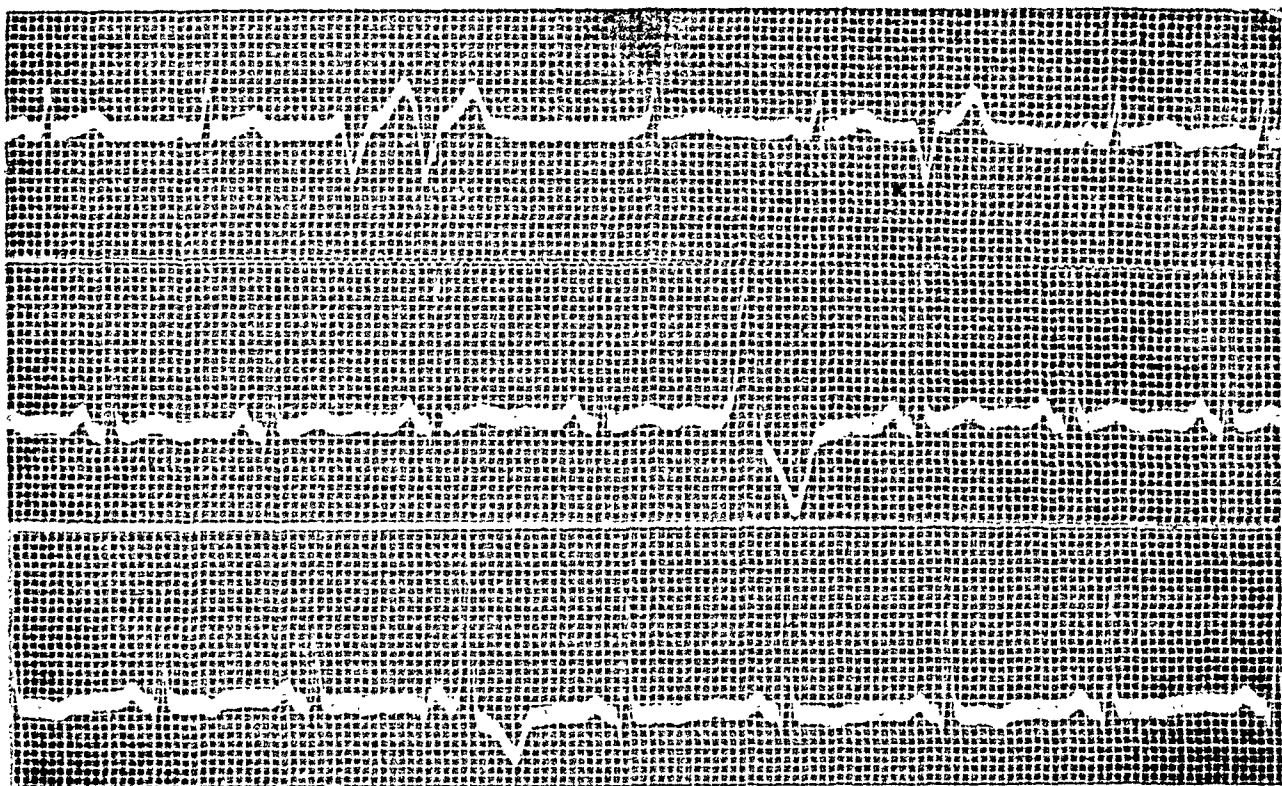
Fig. 1.—C. J. H., Jan. 23, 1943. Shows premature ventricular systoles. Note the two successive ones in Lead I.

He was told to report any further attacks, and, on Feb. 16, 1943, he returned to the hospital. He complained again of successive attacks of dizziness, fullness in the neck, and fainting. He did not complain of precordial pain or respiratory distress. It should be noted that while he complained of palpitation occasionally, this was never a major subjective symptom.

Examination at this time again disclosed the frequent premature systoles, but, more than that, runs of tachycardia were also noted. A long tracing of Lead II was taken. Fig. 2 shows a characteristic portion of that tracing. The upper strip shows the premature ventricular systoles. The lower strip shows unidirectional paroxysmal ventricular tachycardia, lasting 5.2 seconds. Characteristically, the attacks began abruptly and ended abruptly, giving place to sinus
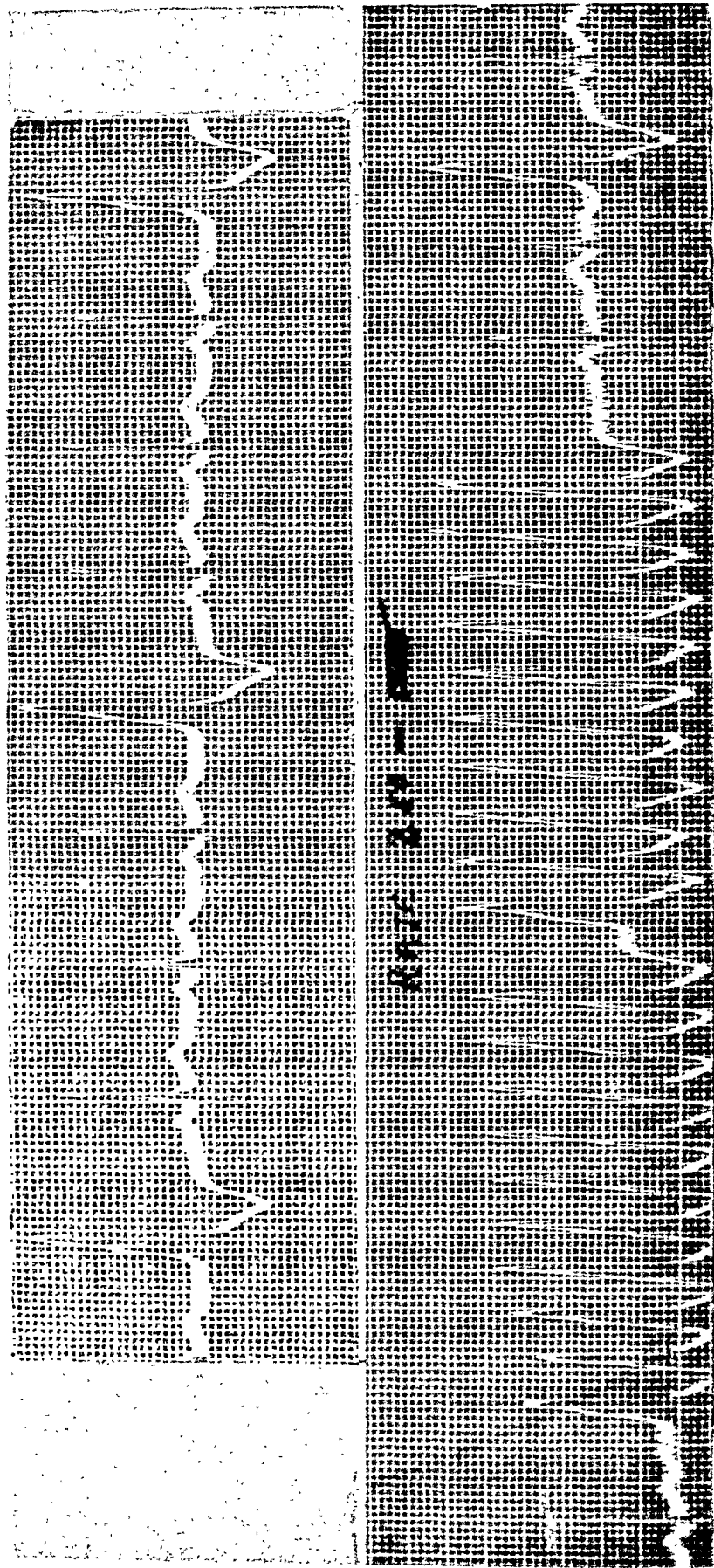
FIG. 2.—C. J. H., Feb. 16, 1913. Lead II shows a run of paroxysmal ventricular tachycardia lasting 5.2 seconds. The upper strip is part of the same lead taken at the same sitting.

rhythm with occasional premature ventricular systoles. Many attacks were recorded on this long tracing; the longest is reproduced here.

On March 12, 1943, another tracing showing attacks of paroxysmal ventricular tachycardia was obtained. In this tracing, the attacks were recorded in the three limb leads and in CF_4 (Fig. 3). If the ectopic ventricular beats in this tracing are compared with those of Fig. 1, it will be noted that there is a close resemblance between the complexes of the tachycardia and the premature ventricular systoles.
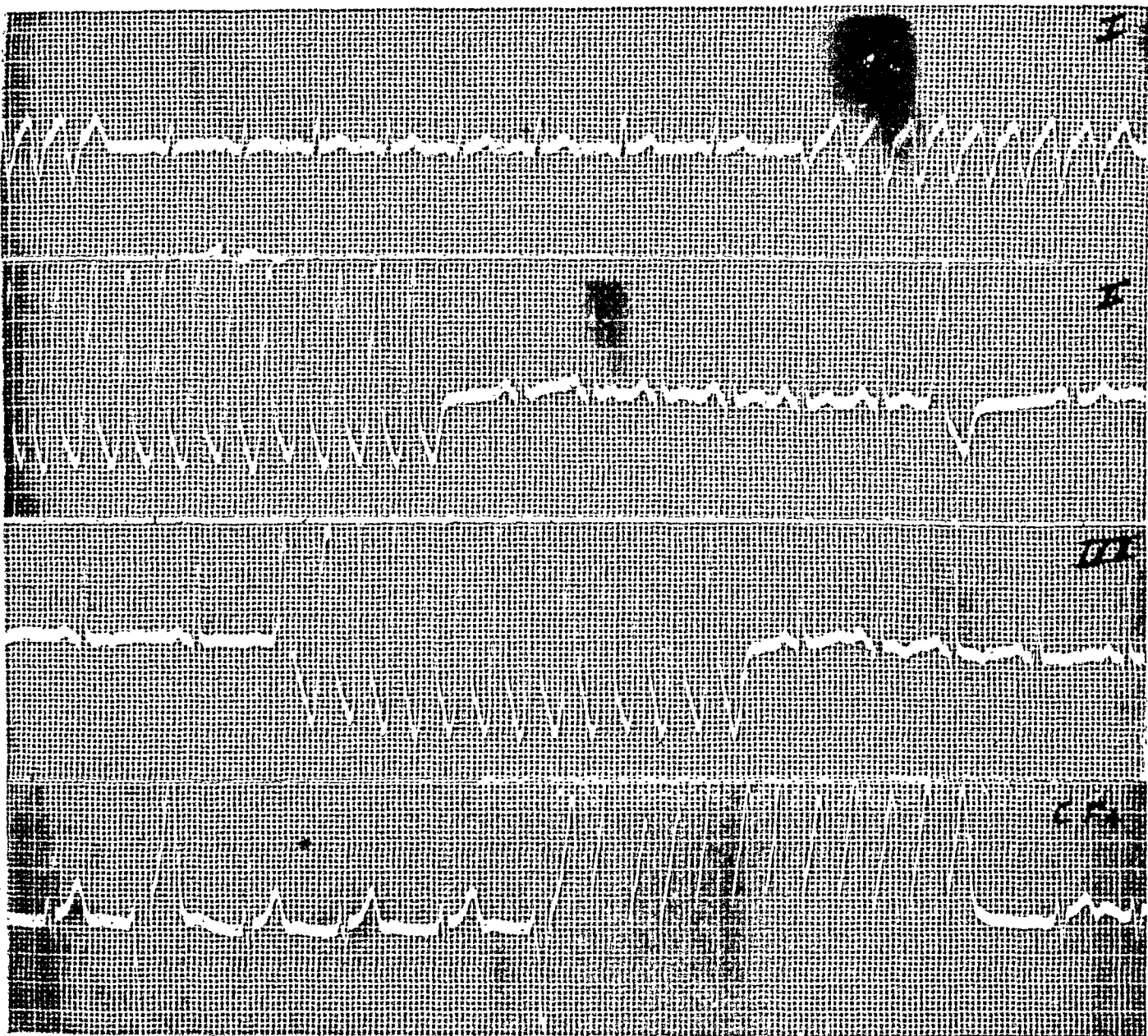
Fig. 3.—C. J. H., March 15, 1943. Runs of paroxysmal ventricular tachycardia in the three limb leads and CF_4. Note resemblance of ventricular complexes to those in Fig. 1, especially in Lead I.

It is believed, therefore, that the focus of origin of the attacks of tachycardia was the same as that which gave rise to isolated premature systoles.

During the recording on March 15 the patient did not faint, but was frequently on the verge of losing consciousness. Evidently no attack was long enough to seriously impair cerebral circulation. Furthermore, the patient was lying flat on the examining table.

Laboratory Data.—Urine: normal except for occasional leucocytes. Erythrocyte count: 4,777,000; hemoglobin, 90 per cent. Nonprotein nitrogen, 39 mg. per cent; sugar, 82 mg. per cent. Basal metabolic rate: (a) ±20 per cent, (b) −3 per cent. Chest roentgenogram: "The heart is of moderate size; there is no apparent enlargement, and the general contour as seen in the A-P view appears normal. The arch of the aorta is within normal limits." The pulmonic area was normal.
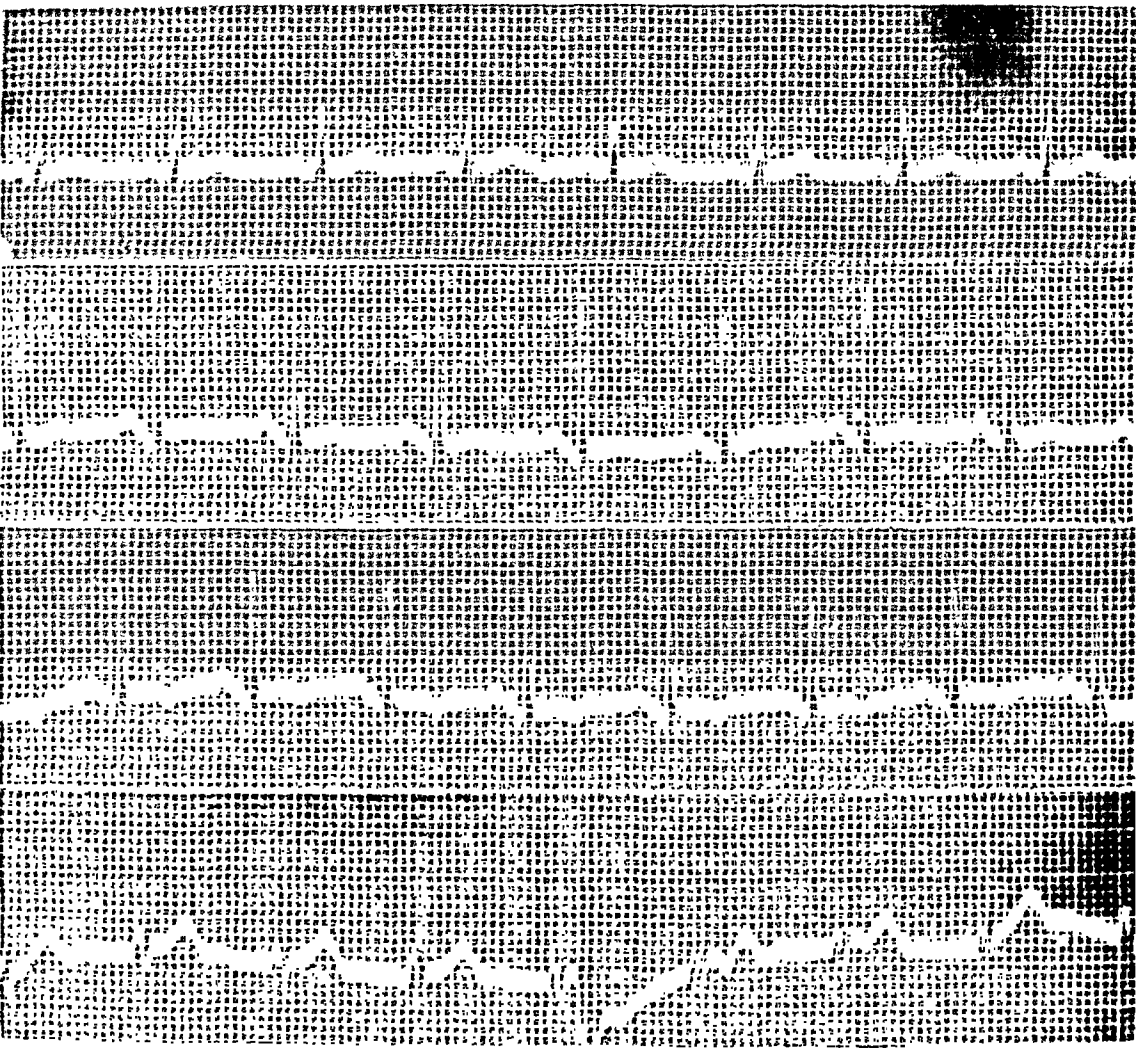
Fig. 4.—C. J. H., May 4, 1943. Shows effect of quinidine sulfate therapy. Note the absence of premature ventricular systoles and the effect of the drug on the T waves.

On March 19, 1943, quinidine sulfate therapy was started. The patient was given the drug first in test doses, and then in larger doses. On March 22 the dose was 18 grains a day, and this was established as an adequate maintenance dose. Daily examinations for weeks during quinidine therapy have shown occasional premature ventricular systoles which seem to have become rarer with the passage of time. On March 25 a tracing showed only one premature ventricular systole. Tracings were taken frequently to note the effects of the quinidine, and, after a reduction of the dose to 15 grains a day, a tracing taken April 3, 1943, showed more frequent premature ventricular systoles,

and, in Leads III and CF$_4$, there were two consecutive premature ventricular systoles. The dosage was raised to 18 grains again. Since then, the patient has had no attacks of paroxysmal ventricular tachycardia and no syncope. Fig. 4 shows a tracing taken May 4, 1943, after forty days of quinidine therapy. Note that there are no ectopic systoles; the effect of quinidine on the T waves is apparent. The patient has had no symptoms of quinidine toxicity.

SUMMARY

1. A case of paroxysmal ventricular tachycardia is described; this occurred in a male soldier, aged 27 years, who had no organic heart disease.

2. Electrocardiograms are presented showing (a) premature ventricular systoles, (b) attacks of paroxysmal ventricular tachycardia which stemmed from the same source as the premature ventricular systoles, and (c) the effects of quinidine sulfate.

3. The efficacy of quinidine sulfate in the prevention of paroxysmal ventricular tachycardia is demonstrated.

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The leucocyte count was 19,000, of which 90 per cent were polymorpho-
nuclears. The urine had a specific gravity of 1.012; it contained a
trace of albumin and an occasional leucocyte. The nonprotein nitrogen
was 41 mg. per cent, and the blood sugar was 110 mg. per cent.

An electrocardiogram (Fig. 1) revealed auricular fibrillation with
a rapid ventricular rate and occasional ventricular premature contrac-
tions. There was depression of the RS-T segments in Leads I and II,
and elevation in Lead III. The T waves were inverted in Leads I and
II. These findings were interpreted as indicating a recent posterior
myocardial infarction.

The patient was placed at absolute rest and was given morphine and
oxygen. His condition improved somewhat during the next two days,
but the pain never entirely disappeared. On the third hospital day he
suddenly became worse and died.

The clinical diagnosis was coronary occlusion with posterior myocar-
dial infarction.

AUTOPSY

A complete autopsy was performed sixteen hours after death. The
significant findings were limited to the heart. The body was that of a
well-developed, well-nourished white man. The heart was greatly en-
larged and weighed 1,050 grams. The left ventricle was greatly hyper-
trophied, and its wall measured 2.5 cm. in thickness. The right ven-
tricle was also hypertrophied, its wall measuring 0.6 cm. in thickness.
The valves were normal. The coronary arteries were patent through-
out their course; there was a moderate degree of sclerosis, but in no
place was the lumen narrowed significantly. There was no gross evi-
dence of myocardial infarction. The myocardium was pale and flabby.

Microscopic examination of the heart muscle revealed considerable
variation in the size of the muscle fibers. Many fibers were greatly
hypertrophied, and others appeared smaller than normal. There was
some increase in the interstitial connective tissue. Sections taken from
the posterior wall of the left ventricle showed a small area of recent
necrosis with early fibrosis. There was no evidence of coronary occlu-
sion in the sections examined. The other organs showed no significant
changes except for a moderate degree of passive congestion.

COMMENT

The outstanding feature of this case was the massive hypertrophy
of the heart, which weighed 1,050 grams. The cause of this great en-
largement was not apparent. There was no valvular disease, no hyper-
tension of any significant degree, no congenital defect, and no other
condition which is commonly associated with cardiac hypertrophy.

The edge of the liver was palpable 4 cm. below the right costal margin. There was evidence of peripheral arteriosclerosis, but no edema.

Emergency treatment consisted of morphine sulfate (⅙ grain), atropine sulfate (¹⁄₁₅₀ grain), papaverine hydrochloride (1 grain), and the use of an oxygen tent. The patient had a leucocytosis of 13,000, with a polymorphonuclear count of 90 per cent. The erythrocyte sedimentation rate was 18 mm. in one hour (our normal, 9 mm.). An electrocardiogram at this time showed a relatively rapid tachycardia, with left bundle branch block. During the first few days the patient's condition remained critical. Gallop rhythm persisted. Dyspnea and cyanosis were marked. The blood pressure fell to 110/70, and moisture appeared at the bases of both lungs. The patient was slowly digitalized, and soon appeared and felt much improved. Convalescence was uneventful until the evening of Dec. 11, 1942, when he developed, while speaking to his relatives, sudden, flaccid, right-sided hemiplegia, with aphasia. The intravenous administration of a grain of papaverine resulted in the return of speech in two or three minutes, and he was soon able to move his right arm and leg. By the next day, no residual signs remained. On Dec. 20, 1942, the patient enjoyed a hearty breakfast and sat up in bed to read a newspaper. Twenty minutes later he was found dead.

Autopsy was performed two hours after death. The heart weighed 1,150 grams. The left ventricular wall varied from 21 to 26 mm., and the right ventricular wall, from 5 to 6 mm., in thickness. Moderate coronary atherosclerosis was present, but the lumina of the vessels were very wide; the coronaries measured as much as 1 cm. in circumference. There was no evidence of occlusion. On the lateral aspect of the left ventricle an area of necrosis and mucoid degeneration, with hemorrhage, approximately 3 cm. in diameter, was seen. The cardiac musculature showed moderate fibrosis, especially near the apex. The papillary muscles were markedly hypertrophied and fibrotic.

Microscopic sections of the heart muscle showed hypertrophy of all fibers. The amount of fibrous interstitial tissue was increased, and active fibroblastic proliferation was present. There was no evidence of perivascular inflammation. Sections of the area of myocardial necrosis revealed degeneration and necrosis of muscle fibers, invasion by fibroblasts, and early collagen deposition and lymphocytic infiltration.

COMMENT

A case of massive cardiac hypertrophy is presented, in which there were no valvular lesions or other possible causes for the enlargement. In considering the diagnostic possibilities, for the sake of completeness, at least, one should not forget myocarditis of unknown origin, as described by Fiedler,[2-4] which occurs with no other demonstrable disease that can be correlated with the cardiac state. The appearance of this type of interstitial myocarditis in apparently healthy persons who more or less suddenly develop progressive myocardial failure has been described by a number of other investigators. Such patients are prone to suddenly develop dyspnea, cyanosis, tachycardia, weakness, and to die suddenly, as was the case with our patient. In most of the cases reported, however, the patients were between the ages of 20 and 50 years. Microscopic examination of these hearts shows diffuse infiltra-

tion of interstitial tissue by lymphocytes, monocytes, and, to a lesser degree, polymorphonuclear, eosinophile, and plasma cells. Numerous fibroblasts and new blood vessels are also observed. The pathologic and histologic picture in our case was not that of myocarditis. The athletic history of the patient may have had some bearing. The case is of unusual interest, not only because of the size of the heart, but because of the absence of explanatory pathologic changes within the heart itself or elsewhere.

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2. Bartels, E. C., and Smith, H. L.:   Gross Cardiac Hypertrophy in Myocardial Infarction, Am. J. M. Sc. 184: 452, 1932.
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Abstracts and Reviews

Selected Abstracts

Lange, K., and Linn, J. B.: Use of Fluorescein Method in Establishment of Diagnosis and Prognosis of Peripheral Vascular Diseases. Arch. Int. Med. 74: 175, 1944.

Fluorescein, when injected intravenously, can be made visible by a beam of long wave ultraviolet radiation on reaching any area of exposed skin or mucous membranes with the blood stream.

The physical prerequisites for a good visualization of fluorescein in the tissue and capillaries are the use of an appropriate long wave ultraviolet ray source and a darkroom. A photoelectric method to indicate the arrival of the dye and to measure the intensity of staining may also be used.

Fluorescein is not toxic. Over 1,000 patients have been examined by this method without untoward reactions, except that 11 patients had vomiting of short duration during the injection. Experiments on animals showed extremely low toxicity. The dye travels with the blood stream and diffuses immediately through the capillaries into the interstitial spaces. Dead cells do not stain. Fluorescein is partly adsorbed to the plasma proteins. Pathologic changes in plasma proteins do not change the amount of fluorescein immediately available for diffusion.

Ultrafiltration experiments show that the amount of dye diffusing into the tissue depends on intracapillary pressure; if the latter rises, the amount which diffuses into the tissue with the water increases without changing the concentration. Changes in capillary permeability change the amount which diffuses as well as the concentration. Even slight inflammation increases the fluorescence of the tissue. Pigmentation, especially in colored people, makes the test unreliable, although certain basic facts can still be elicited. The degree of fluorescence depends on the amount of blood flowing through a certain part of the body. Objective determinations of circulation time in normal persons showed that the circulation time between the arm and the lips is between fifteen and seventeen and one-half seconds, while the time to the legs normally should not exceed twice this figure.

Nine patients with acute embolism of the legs were examined. It was possible to define exactly the lowest possible level of amputation as far as the skin is concerned and to decide immediately on the probable formation of sufficient collateral circulation to avoid amputation.

Block of the sympathetic lumbar ganglions should be performed to avoid mistakes caused by vasospasm.

The immediate diagnosis of thrombotic occlusion can also be made.

Small gangrenous areas in arteriosclerotic peripheral vascular disease can be judged as to the prospect for healing, localization, or further spread.

There are two functional types of arteriosclerotic peripheral vascular disease as shown by this test. The first form concerns the larger vessels, mainly causing rapidly spreading gangrene in the periphery, while the other occludes mainly small arteries with capillaries, thereby not necessitating large amputations.

Thromboangiitis obliterans has usually a higher fluorescence than one would expect from the lack of arterial pulsations. This discrepancy is a leading sign. Spotty fluorescence may complete the picture.

Vasospastic disorders have a low fluorescence during the attack, which immediately returns to normal or even increases above normal on blockage of the sympathetic chain.

Rubor on an inflammatory basis in a limb with arteriosclerotic peripheral vascular disease can be well differentiated from venous congestion (rubor on dependency).

Thrombophlebitis of superficial vessels can be well made out as long as it is inflammatory and the extent of the inflammation can be outlined.

Ulcers of the leg on a varicose vein basis can be judged as to their outlook for healing and skin grafting. Syphilitic ulcers of the leg have a specific picture in the fluorescein test which distinguishes them from varicose vein ulcers.

AUTHORS.

Bain, C. W. C.:   Incomplete Bundle Branch Block.   Brit. Heart J. 6: 139, 1944.

Six cases of incomplete bundle branch block have been described. In none did the duration of the QRS exceed 0.10 second when incomplete bundle branch block was judged to be present. In all of the cases normal complexes have been present for comparison, either in the same record or within a short period.

The evidence suggests that the cases could be divided into three groups.

The first shows a slight increase in the QRS without axis deviation as exemplified by the aberrant ventricular response to an auricular premature systole. These are probably due to a bilateral delay down each main branch (Case 1).

The second shows delay down one branch, fulfilling the criteria for bundle branch block except that the QRS does not exceed 0.10 sec. (Cases 1, 2, 3, 4 and 6).

The third shows transitional complexes (Cases 5 and 6). In these cases it is likely that the transitional complexes were due to a combination of bilateral delay down each main branch with additional delay down one branch, since both cases had an unstable branch block which sometimes changed from right to left, and there was not much axis deviation, although the QRS duration was 0.10 second.

AUTHOR.

Hume, W. E., and Szekely, P.:   Cardiac Involvement in Spirochaetal Jaundice.   Brit. Heart J. 6: 135, 1944.

The authors report a case of spirochetal jaundice with electrocardiographic evidence of transient myocardial involvement. For five days following admission the electrocardiogram showed auricular fibrillation and a sinus rhythm with T-wave changes, all of which had disappeared four months later. It is believed that, if more extensive studies were made in cases of jaundice, especially those with very low blood pressure and changes in the character of the heart sounds, more instances of myocardial involvement might perhaps be encountered.

The authors believe that the electrocardiographic changes can be accounted for by direct involvement of the heart either in the form of multiple hemorrhages or of toxic damage to the heart muscle, or both.

AUTHORS.

Bramwell, C., and Jones, A. M.:   Acute Left Auricular Failure.   Brit. Heart J. 6: 129, 1944.

Two cases of mitral stenosis with acute pulmonary edema leading to death about the middle stage of pregnancy are described.

The mechanism of production of this complication is discussed and it is attributed to acute left auricular failure.

AUTHORS.

Rich, A. R., and Gregory, J. E.: Further Experimental Cardiac Lesions of the Rheumatic Type Produced by Anaphylactic Hypersensitivity. Bull. Johns Hopkins Hosp. 75: 115, 1944.

In preceding papers we have described and illustrated cardiac lesions of the rheumatic type that were produced in animals by hypersensitive reactions to foreign protein; shown the basic identity of rheumatic pneumonitis with the pneumonitis resulting from sulfonamide hypersensitivity in nonrheumatics; and assembled evidence of a variety of other types in support of the view that human rheumatic lesions represent the results of focal hypersensitive reactions. In the present paper further experimental cardiac hypersensitive lesions of the rheumatic type are illustrated. Studies illustrating experimental hypersensitive pneumonitis and arthritis will be presented shortly.

AUTHORS.

Wilson, M. G., and Lubschez, R.: Recurrence Rates in Rheumatic Fever: The Evaluation of Etiologic Concepts and Consequent Preventive Therapy. J. A. M. A. 126: 477, 1944.

The expected risk for a major recurrence of rheumatic fever at specific ages from 4 to 25 years and for various patterns of disease was defined from the analysis of the records ·of 499 rheumatic individuals during 5,677 person-years of life experience.

The only factors which were found to influence the risk of future recurrences were age and the interval of time elapsing since the last attack.

Most published studies on the relative frequency of rheumatic fever in experimental and control groups do not appear to meet the basic requirements for adequate biostatistical analysis. Final judgment as to the validity of etiological concepts and consequent preventive therapy, which are based on these studies, must be deferred.

AUTHORS.

Jones, T. D.: The Diagnosis of Rheumatic Fever. J. A. M. A. 126: 481, 1944.

For the present, it would seem advisable to limit the diagnosis of rheumatic fever to patients with rather distinct clinical manifestations. It is suggested that the following constitute reasonably certain diagnostic criteria:

Any combination of the major manifestations (carditis, arthralgia, chorea, nodules, and a verified history of previous rheumatic fever).

The combination of at least one of the major manifestations with two of the minor manifestations (fever, abdominal or precordial pain, erythema, marginatum, epistaxis, pulmonary changes, and laboratory abnormalities).

The presence of rheumatic heart disease increases the diagnostic significance of the minor manifestations when no other cause for these manifestations exists.

Small though probably insignificant errors may be found with these criteria. Numerous clinical entities as enumerated may be confused with rheumatic fever. Clinical observations and, wherever possible, specific diagnostic tests should be applied in any diagnostic problem.

AUTHOR.

Van Ravenswaay, Arie C.: The Geographic Distribution of Hemolytic Streptococci: Relationship to the Incidence of Rheumatic Fever. J. A. M. A. 126: 486, 1944.

Bacteriologic studies at eight Army Air Forces installations during the period from Jan. 1 to April 21, 1944, reveal that Group A hemolytic streptococci isolated

from cases of upper respiratory disease, scarlet fever, and acute rheumatic fever belonged to a multiplicity of Lancefield types.

At none of the posts studied was a single epidemic strain responsible for the streptococcic disease observed.

At the posts studied, bacteriologic data obtained after the development of acute rheumatic fever were not applicable to the preceding upper respiratory infections.

An apparent correlation was observed between post survey (carrier) rates from Group A hemolytic streptococci, incidence rates for scarlet fever, and the incidence of acute rheumatic fever.

AUTHOR.

Thomas, C. D.: Prevention of Recurrences in Rheumatic Subjects. J. A. M. A. 126: 490, 1944.

The belief is expressed that, in spite of the difficulties involved, the increasingly widespread use of prophylactic sulfonamides will bring tremendous advance in the problems of rheumatic fever and rheumatic heart disease.

AUTHOR.

Rutstein, D. D.: The Role of the Cardiac Clinic in the Rheumatic Program. J. A. M. A. 126: 484, 1944.

A community rheumatic fever program is essential if complete care is to be given to patients suffering from rheumatic disease, and the cardiac clinic with an affiliated registry should serve as the focus around which the community rheumatic fever program should be built.

AUTHOR.

Wellen, I., Welsh, C. A., and Taylor, H. C.: The Effect of Pregnancy and Renal Function in Women With Pre-Existing Essential Hypertension and With Chronic Diffuse Glomerulonephritis. J. Clin. Investigation 23: 742, 1944.

Renal function studies made upon patients with essential hypertension indicate that pregnancy is associated with a slight temporary increase in renal blood flow. Glomerular filtration rate and the tubular excretory mass (Diodrast Tm) are unaffected by pregnancy in these women.

Comparison of results obtained during pregnancy and for an observation period of one to four years after delivery indicate that pregnancy itself, when uncomplicated by specific toxemia, does not cause any deterioration of renal function in women with essential hypertension or chronic glomerulonephritis.

AUTHORS.

Rappaport, M. B., and Luisada, A. A.: Indirect Sphygmomanometry. A Physical and Physiologic Analysis and a New Procedure for the Estimation of Blood Pressure. J. Lab. & Clin. Med. 29: 638, 1944.

An apparatus is described which can register graphically and simultaneously all of the physiologic phenomena which must be evaluated for the estimation of blood pressure by the palpatory, oscillatory, and the auscultatory methods. This graphic device eliminates the human element with its subjective differences in the appreciation of the physiologic signs and makes possible a quantitative comparison of the associated phenomena.

The theoretical principles fundamental to the palpatory, oscillatory, and the auscultatory methods are discussed. With the aid of the above mentioned apparatus, the authors have observed:

1. In an oscillometric curve, the configuration of the pulse wave is modified between the limits of systolic and diastolic pressure. The degree of modification

is a function of the systolic, diastolic, and cuff pressures. The wave form is unmodified only when the cuff pressure is lower than the diastolic pressure level.

2. Diastolic pressure is represented in the oscillometric curve by the first arterial pulsation which is undistorted during its most negative phase.

3. The oscillatory method is reliable in the estimation of the systolic blood pressure only when accurate sphygmographic registrations are made. Inaccurate or poor sphygmograms do not indicate distinctly the initial appearance of the minute wave which represents the beginning of ejection of blood into the artery as differentiated from the surpramaximal oscillations.

4. The gradual tapering-off of the pulse amplitude in an oscillometric curve below the diastolic pressure level commonly described is not a physiologic phenomenon but a definite instrumental error. This is essentially due to a diminution in the efficiency of the cuff as a detector of arterial pulsations when the pressure is lowered. The use of independent pressure and registration cuffs eliminates this source of error.

5. The Korotkow sounds occur simultaneously with the sharp primary oscillation of the brachial pulse which is the beginning of the ejection of blood into the artery.

6. There are two major contributing factors to the production of the Korotkow sounds; the mechanism of each is described.

7. The first distinct Korotkow sound (systolic pressure level) generally occurs simultaneously with the first distinct sharp primary oscillation of an oscillometric curve. The first suddenly diminished Korotkow sound (auscultatory diastolic pressure level) corresponds very closely to the first undistorted arterial pulsation.

8. An explanation is given for the sudden diminution in the intensity of the Korotkow sounds at diastolic pressure.

9. As a general rule, the systolic pressure is underestimated because the first Korotkow sound which appears during a gradual cuff deflation possesses an intensity below human audibility.

10. Diastolic blood pressure as judged by the auscultatory method (when the sounds suddenly become dull and muffled) corresponds exactly with the recorded values and within close limits with the negative transition effect of the oscillometric curve. Any other sound phase does not bear any relationship whatsoever with diastolic pressure.

11. The stethoscopic method of sound registration shows the first Korotkow sounds (systolic pressure level) most distinctly, whereas the logarithmic method registers the sudden diminution (diastolic pressure level) more distinctly than the stethoscopic method.

12. In some instances, the sudden muffling effect at the diastolic pressure level is not audible. In such cases, the graphic method may show this diminution effect with sufficient clarity to accurately estimate the diastolic blood pressure.

13. Considerable error may be introduced when estimating the systolic blood pressure by the palpatory method. The degree of error may be in the order of several millimeters of mercury below the actual value.

14. The diastolic pressure level cannot be estimated by the palpatory method, because the sense of human feeling cannot detect the instant when the arterial pulsation initially attains an undistorted configuration.

The graphic registration method which registers all of the physiologic phenomena associated with indirect sphygmomanometry, has application in the more exact studies of blood pressure. The method shall prove useful in the clarification of such phenomena as the auscultatory gap, the double tone of Traube, the double murmur of Duroziez, the murmur accompanying the pistol shot pulse, etc.

AUTHORS.

de Takats, G.: The Value of Sympathectomy in the Treatment of Buerger's Disease. Surg., Gynec. & Obst. 79: 359, 1944.

Sympathectomy deprives the extremity of its vasoconstrictor tone. It does not influence the course of Buerger's disease. However, when this disease is in an inactive phase and when adequate preoperative tests reveal the presence of sufficient collateral vascular supply, sympathectomy will aid an extremity considerably whose vessels have been crippled by recurrent attacks of segmental thrombosis. In this series of 50 patients 136 sympathectomies have been done; about one-half of those patients have also had minor amputations combined with sympathectomy. Of the 50 patients, 37 have been rehabilitated to full-time work, 7 are doing part-time work, and only 6 are invalids. In addition to foot hygiene and complete abstinence from tobacco, a change of occupation is important for those whose feet are continuously subjected to an exposure to cold or trauma.

AUTHOR.

Benians, T. H. C.: A Vasospastic Factor in the Serum of a Case of Raynaud's Disease With Cold Agglutination Experiments on Rabbits. J. Lab. & Clin. Med. 29: 1074, 1944.

A serum containing high titer cold antibodies, and derived from a case of Raynaud's disease, is shown to cause fatal pulmonary artery spasm in rabbits when given, cold, intravenously. This effect is mitigated by giving the serum warm. It is suggested that these cold antibodies have a direct effect, probably of an allergic type, on arterial musculature both in the experimental animal and the clinical case. It is further suggested that the frequent association of cold antibodies with a Wassermann-like body point to an origin of the former from diseased vascular structures and this again would help to explain their action on both blood cells and vessels. A possible function of cold antibodies in normal vascular control is mentioned, these may or may not be the basis of prototype of the high titer cold antibodies.

Preliminary experiments in protection against the cold antibodies by the intravenous injection of lipoids have been carried out with some success.

AUTHOR.

Taylor, C.: Some Properties of Maximal and Submaximal Exercise With Reference to Physiological Variation and the Measurement of Exercise Tolerance. Am. J. Physiol. 142: 200, 1944.

Thirty-one subjects have been given a test twice, consisting of a four-minute walk on the treadmill and a run to exhaustion after a four-minute, interim rest, the retest following in three days. Heart and respiration rates, ventilation, blood lactate, per cent of oxygen and CO_2, and oxygen consumption were determined during the walk and during the last minute of the run, and the first three of these measures throughout both walk and run. From these data it has been possible to evaluate the sources of variation in the physiologic measures and their validity as indicators of fitness.

AUTHOR.

Fine, J., and Seligman, A. M.: Traumatic Shock. VII. A Study of the Problem of the "Lost Plasma" in Hemorrhagic Tourniquet, and Burn Shock by the Use of Radioactive Iodo-Plasma Protein. J. Clin. Investigation 23: 720, 1944.

Plasma proteins tagged with radioactive iodine were used to study the capillary leakage hypothesis in hemorrhagic, tourniquet, and burn shock. No evidence of leakage due to a change in the permeability of the generalized capillary bed was

found. Tagged plasma proteins escaped into areas of injury in considerable amounts, but not into untraumatized areas. This was also true after plasma infusion.

There is also evidence to show that the general capillary bed does not become more permeable to plasma proteins or plasma in the late or irreversible phase of hemorrhagic shock following transfusion.

Following saline therapy in hemorrhagic shock, plasma proteins are carried out of the blood stream with saline. This occurs to a greater extent in irreversible than reversible hemorrhagic shock. The volume of dilute plasma lost in this way is small.

AUTHORS.

Fine, J., Frank, H. A., and Seligman, A. M.: Traumatic Shock. VIII. Studies in The Therapy and Hemodynamics of Tourniquet Shock. J. Clin. Investigation 23: 731, 1944.

The application of tourniquets to both hind legs of unanestheized dogs for five hours is not always followed by shock. If shock occurs, it is of moderate intensity. Saline solution given intravenously is curative.

The application of tourniquets to unanesthetized dogs for eight to eleven hours will uniformly produce shock which is fatal if untreated. Intravenously administered plasma, 5 per cent bovine albumin in saline solution, or 25 per cent bovine albumin supplemented by peroral fluid are effective therapeutic agents, if the deficiency in plasma volume is made good while the blood pressure is above 60 mm. Hg. Occasionally, they may be effective at blood pressures between 60 and 40 mm. Hg. Physiologic saline, 25 per cent albumin without peroral fluid, and 5 per cent saline with peroral water are not effective.

The critical blood pressure level of tourniquet shock is much higher than that of hemorrhagic shock. This may be related to the deleterious effect on cardiac output of the increased blood viscosity of tourniquet shock. Consequently, the high viscosity requires that plasma or plasma substitutes rather than whole blood be the agent of choice for blood volume replacement therapy.

Effective therapy is always accompanied by a substantial reduction in hematocrit and usually by a substantial restoration of the deficiency in plasma volume.

The course of events following ineffective though adequate blood volume replacement therapy of tourniquet shock is not materially altered by the administration of sodium succinate. Cure of five-hour tourniquet shock, attributed by other investigators to succinic acid, is achieved by saline therapy alone in experiments in which anesthesia is omitted. It is therefore apparent that any value sodium succinate may have demonstrated in studies by other investigators may be attributable to its ability to counteract the depressing effect of barbiturates.

AUTHORS.

Blackman, S. S., Jr., Thomas, C. B., and Howard, J. E.: The Effect of Testosterone Propionate on the Arterial Blood Pressure, Kidneys, Urinary Bladder and Livers of Growing Dogs. Bull. Johns Hopkins Hosp. 74: 321, 1944.

Testosterone propionate given subcutaneously to growing puppies of both sexes for periods of six and fourteen weeks produced effects which are well known in other species of animals. The androgen had little effect on the arterial blood pressure of the dogs.

The liver of each treated dog and the kidneys of the dogs treated for fourteen weeks were enlarged by approximately 11 to 17 per cent. The urinary bladders of the treated dogs were considerably enlarged, due probably to hypertrophy of smooth muscle. No effect of the androgen could be detected on the microscopic appearance of the renal juxtaglomerular tissue.

AUTHORS.

Book Reviews

THE ELECTROCARDIOGRAM. ITS INTERPRETATION AND CLINICAL APPLICATION: By Louis H. Sigler, M.D., Attending Cardiologist and Chief of Cardiac Clinics, Coney Island and Harbor Hospitals, New York. Grune & Stratton, Inc., New York, 1944, 400 pages, 203 illustrations.

This ambitious work is divided into twenty-five chapters in which all phases of electrocardiography are taken up. The text is profusely illustrated with diagrams and photographs of many actual electrocardiograms. The latter, except for a small number, are well chosen and satisfactorily reproduced.

The material in the book is not, in the reviewer's opinion, particularly well organized. In many chapters there are discussions and figures relating to electrocardiographic conditions that are treated elsewhere in detail, and Chapter XVI, entitled "Other Abnormalities in the Electrocardiogram," is largely made up of a curious collection of unrelated tracings, practically all of which might logically be presented in other sections of the book. The author discusses multiple precordial leads in some detail in the final chapter, but fails to refer to leads of this type in earlier sections dealing with myocardial infarction, bundle branch block, and ventricular hypertrophy. This arrangement of material may have advantages, but does not properly emphasize the proved value of these leads in the conditions mentioned. Relative to myocardial infarction and ventricular hypertrophy, the reviewer cannot agree with the following statement, made on page 390: In cases of infarction, or in those of ventricular preponderance in which the standard leads show specific changes, there is, as a rule, no need of wasting time in obtaining any of the precordial leads." From the standpoint of diagnosis alone, multiple precordial leads may be unnecessary when one is dealing with infarction. Such leads are, nevertheless, of great value when patients have anterior infarcts because they give information relative to the size of the lesion, and this has obvious bearing on the prognosis. Furthermore, multiple precordial leads are frequently necessary to decide whether right or left axis deviation in the standard leads is due to hypertrophy of the right or left ventricle or is caused by a peculiarity in the position of the heart.

Chapters I and II, concerned with equipment and methods for taking electrocardiograms, are not as complete as could be wished and contain a number of minor inaccuracies.

The discussion of bundle branch block, in Chapter XV contains some statements that are open to question. The view of the author that the QRS interval must be over 0.13 second before complete branch block can be considered to be present is certainly not a generally accepted one, and the suggestion that a large part or all of a bundle branch supplying one ventricle must be damaged before complete bundle branch block can occur is not in accord with experimental facts.

The chapters concerned with the cardiac arrhythmias are satisfactory, and the sections dealing with trauma of the heart and the electrocardiogram in various states contain much worth-while material not fully treated in other books on this subject.

The author must be complimented on his conservative attitude, expressed in the preface, relative to the role that the electrocardiogram should play in the diagnosis of heart disease. Although this book cannot be heartily recommended for the dis-

cussions relating to the physical basis of the electrocardiogram or for the fundamental approach that has been employed, it has many attractive features and should be of value to students of electrocardiography.

F. D. JOHNSTON.

A BIBLIOGRAPHY OF AVIATION MEDICINE, SUPPLEMENT: By Phebe Margaret Hoff, Ebbe Curtis Hoff, and John Farquhar Fulton. Committee on Aviation Medicine, Division of Medical Sciences, National Research Council, 1944, 77 pages, plus keys and indexes, 2,336 entries, $2.50.

This supplement brings its rapidly expanding subject up to date, and maintains the high standard of the original *Bibliography* (cf. AM. HEART J. 24: 577, 1942).

HORACE M. KORNS.

Books Received

PUBLICACIONES CEL CENTRO DE INVESTIGACIONES TISIOLOGICAS. Director: Professor Roque A. Izzo. Volume vii, Pabellon ''Las Provincias,'' Buenos Aires, 1943, 462 pages.

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

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The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

Executive Committee.

AMERICAN HEART JOURNAL

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